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The kinetics of the decomposition of the addition compounds formed by sodium hydrogen sulphite and a series of aldehydes and ketones. Part II. General discussion of energy–entropy relationships. By D. A. Blackadder and Sir Cyril Hinshelwood

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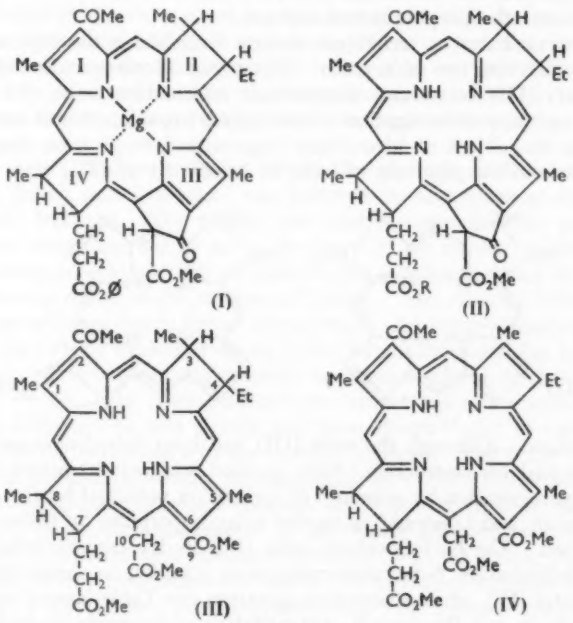
*o*-Hydroxybenzenesulphonamide. By C. A. Bartram, P. Oxley, D. A. Peak, and J. S. Nicholson

# 355. *Chlorophyll and Related Compounds. Part VII.* The Structure of Bacteriochlorophyll.*

By J. H. Golden, R. P. Linstead, and G. H. Whitham.

Hans Fischer's structure for bateriochlorophyll (I) has been strengthened and some aspects of its stereochemistry have been elucidated. Stepwise dehydrogenation of a bacteriochlorophyll derivative to the corresponding chlorin and porphin is described, together with some observations on the light absorption of the pigments.

The red and the purple photosynthetic bacteria contain, in addition to carotenoids, one chlorophyll component, bacteriochlorophyll, which appears to be associated in the cell with different proteins. The chlorophyllic component of the green sulphur bacteria appears to be a different substance.




The chemistry of bacteriochlorophyll has been extensively investigated by Fischer and his co-workers. Their structure [1] (I) is supported by evidence which may be summarised as follows: Conversion into bacteriochlorin $e_6$ trimethyl ester (III) *via* bacteriomethylphæophorbid (II; R = Me), analogous to similar transformations of chlorophyll-*a*, was followed by dehydrogenation [2] to the chlorophyll derivative (IV). Partial synthesis of this compound (IV) from chlorophyll [3] demonstrated that bacteriochlorophyll is a partially hydrogenated chlorophyll-*a* bearing an acetyl group at position 2 in place of a vinyl group.

* Part VI, *J.*, 1957, 733.

[1] Fischer-Orth, "Die Chemie des Pyrrols," Akademische Verlagsges., Leipzig, 1940, Vol. II, Part 2, p. 305.

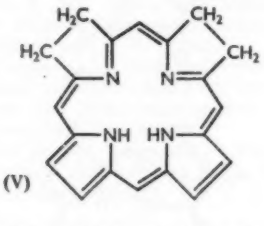
[2] Fischer, Lambrecht, and Mittenzwei, *Z. physiol. Chem.*, 1938, **253**, 1.

[3] Fischer, Lautsch, and Lin, *Annalen*, 1938, **534**, 1.

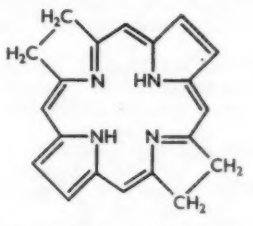
The precise level of hydrogenation of bacteriochlorophyll was not determined although it was assumed to be the tetrahydroporphin (dihydrochlorin), shown in the formulæ.

The two " extra " hydrogen atoms in chlorophyll have been proved [4] to be in ring (IV). As to the location of the assumed second pair of " extra " hydrogen atoms in bacteriochlorophyll direct evidence is scanty and interpretation conflicting. Mittenzwei [5] suggested ring II on the grounds that oxidative degradation of a bacteriochlorophyll derivative yielded small amounts of an oil which was believed to be ethylmethylsuccinic anhydride, which was not obtained on oxidation of chlorophyll-*a* derivatives. Seely [6] criticised this deduction and made the improbable suggestion that the ethylmethylsuccinic anhydride arose from ring IV, by decarboxylation of the propionic acid side-chain. Seely proposed that the " extra " hydrogen atoms are on ring I or III, probably the latter. Barnard and Jackman [7] recently obtained important theoretical evidence which bears on this problem. Their molecular-orbital calculations on the position of the longest-wavelength band in the absorption spectra of the two possible types of tetrahydroporphins (V) and (VI) supported a structure of type (VI) for bacteriochlorophyll. Eisner's recent work [8] on the hydrogenation product of octaethylporphin is also relevant.

The present work, based on techniques already successful in the chlorin and the chlorophyll field, is divided into two main parts; (i) stepwise dehydrogenation of bacteriochlorin $e_6$ trimethyl ester (III) to provide unequivocal information as to the precise level of hydrogenation, and (ii) re-investigation of the degradative oxidation of bacteriochlorophyll derivatives with the object of identifying fragments derived from ring II. The light absorption of some of the pigments will also be briefly discussed.




(V)




(VI)

*Dehydrogenations.*—Although the ester (III) had been dehydrogenated to the chlorin (IV) by Fischer and his co-workers [2] their method was not attractive for quantitative purposes. Dehydrogenation by quinones of high redox potential by the general methods of Braude, Jackman, and Linstead,[9] as applied to hydroporphins by Eisner and Linstead,[10] was therefore used. The bacteriochlorin ester (III) in dry benzene solution at 20° with one mol. of 2 : 3-dichloro-5 : 6-dicyanobenzoquinone afforded an almost quantitative yield of the dihydro-ester (IV), whose absorption spectrum (see Table) agreed satisfactorily with that quoted by Stern and Pruckner.[11] Quantitative experiments showed unambiguously that the bacteriochlorophyll series contains two more hydrogen atoms than the chlorophyll series.

It is of interest that only one dehydro-compound is formed since *a priori* it might be expected that either the pair of hydrogen atoms characteristic of bacteriochlorophyll (in ring II?) or those in ring IV would be abstracted by the quinone. Indeed it could not quite be taken for granted that the hydrogen would come off in 1 : 2-pairs and not in some other way. Consideration of the model for ester (III) shows that in the transition state

[4] Ficken, Johns, and Linstead, *J.*, 1956, 2272.
[5] Mittenzwei, *Z. physiol. Chem.*, 1942, **275**, 93.
[6] Seely, U.S. Atomic Energy Commn., 1953, U.C.R.L., 2417.
[7] Barnard and Jackman, *J.*, 1956, 1172.
[8] Eisner, *J.*, 1957, 3461.
[9] Braude, Jackman, and Linstead, *J.*, 1954, 3548.
[10] Eisner and Linstead, *J.*, 1955, 3749.
[11] Stern and Pruckner, *Z. phys. Chem.*, 1939, **185**, *A*, 140.

for dehydrogenation of ring IV the methylene group attached to position 7 must become coplanar with the macrocyclic ring, resulting in considerable steric compression between this methylene group and $C_{(10)}$ (also coplanar). Such compression is not involved in the transition state for dehydrogenation of ring II which is not flanked by a *meso*-substituent.

Further dehydrogenation of the acetylchlorin (IV) by the dichlorodicyanoquinone was slow, even at raised temperatures. However, this provided a convenient preparation of the corresponding porphin, oxochloroporphyrin $e_6$ trimethyl ester,[12] when excess of quinone was used. A quantitative study was impracticable owing to the fairly rapid rate of destruction of the quinone under these conditions.

The copper derivative of the acetylchlorin (IV) proved to be more readily dehydrogenated and was amenable to quantitative study, which showed that two hydrogen atoms are abstracted in conversion to the porphin level. It is believed that this represents the first quantitative dehydrogenation of a natural chlorophyll derivative, although it has already been realised with the simple chlorins.[10]

*Oxidative Degradation.*—The ester[13] (III) was chosen as the most suitable bacteriochlorophyll derivative for degradation as it could be fairly readily obtained in a chromatographically pure, crystalline state. If structure (III) is correct then by analogy with similar oxidations of macrocyclic pigments[4,14] it would be expected that oxidative degradation of ester (III) should lead to ethylmethylsuccinimide from ring II, and dihydrohæmatinimide from ring IV. Rings I and III would be expected to undergo more extensive degradation.

Oxidation of ester (III) by chromium trioxide in sulphuric acid under the conditions used by Ficken, Johns, and Linstead[4] was followed by separation of the product into neutral and acidic fractions. The neutral fraction was examined by paper chromatography, the spots being detected by an imide spray:[15] an intense doublet was formed, corresponding closely to ethylmethylsuccinimide plus ethylmethylmaleimide, in addition to a faint spot corresponding to dihydrohæmatinimide. The ethylmethylmaleimide could arise by dehydrogenation of ring II before degradation. An infrared spectrum of the crude neutral fraction (in $CHCl_3$) exhibited strong imide bands but none due to an anhydride, showing that under our conditions no detectable amounts of ethylmethylsuccinic anhydride were formed (cf. ref. 5). The imide mixture was hydrolysed to the corresponding acids by concentrated hydrochloric acid (which had been shown[16] not to cause inversion of configuration at the carbon atoms α to the carboxyl groups). The crude hydrolysate was treated with cold neutral potassium permanganate to destroy ethylmethylmaleic acid (ethylmethylsuccinic acid and dihydrohæmatinic acid were shown to be unaffected under these conditions). Paper chromatography of the residue afforded spots probably corresponding to dihydrohæmatinic and ethylmethylsuccinic acid. Further, conversion of the mixed acids into their di-*p*-bromophenacyl esters followed by chromatography on neutralised alumina gave a crystalline *p*-bromophenacyl ester, the infrared spectrum (KBr disc) of which was identical with that of synthetic di-*p*-bromophenacyl *transoid*-ethylmethylsuccinate[16,17] and characteristically different from that of the *cisoid*-ester. This *p*-bromophenacyl ester was optically active, showing that racemisation had not occurred during the manipulations and therefore (as in the case of chlorophyll and its degradation products) the *transoid*-configuration of the acid represents the configuration in the ester (III), *i.e.*, the hydrogen atoms in ring II are *trans*-orientated.

Paper chromatography of the acid fraction from the oxidation gave a spot corresponding to dihydrohæmatinimide. Hydrolysis of the imide mixture and permanganate oxidation as before was then followed by paper chromatography; a strong spot corresponding to

[13] Fischer and Riedmair, *Annalen*, 1933, **505**, 87.
[12] Fischer and Hasenkamp, *ibid.*, 1935, **515**, 148.
[14] Muir and Neuberger, *Biochem. J.*, 1949, **45**, 163; 1950, **47**, 97.
[15] Reindel and Hopper, *Chem. Ber.*, 1954, **87**, 1103; Rydon and Smith, *Nature*, 1952, **169**, 922.
[16] Golden and Linstead, following paper.
[17] See Ficken, Johns, and Linstead, *J.*, 1956, 2280, for nomenclature.

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dihydrohæmatinic acid was obtained, besides other spots probably due to oxalic and succinic acid.

These results are in complete agreement with structure (III) for bacteriochlorin $e_6$ trimethyl ester and provide the further information that the hydrogen atoms in ring II are *trans*-orientated. That the hydrogen atoms in ring IV are also *trans* to one another follows from the conversion of ester (III) into the chlorophyll-*a* derivative (IV) and the earlier proof by Ficken, Johns, and Linstead [4] that in chlorophyll-*a* the hydrogen atoms in ring IV are *trans*-orientated. It is not possible to assign the relative configuration of the hydrogen atoms in ring II to those in ring IV on the known evidence: this would require a knowledge of the absolute configuration of the two rings. The only remaining stereochemical point is the configuration of the 10-methoxycarbonyl group in bacteriochlorophyll. Since the hydrogen atom at position 10 is very powerfully activated by three electron-attracting groups the 10-methoxycarbonyl group might be expected to be in the thermodynamically more stable configuration, *viz.*, *trans* to the propionic acid side-chain in ring IV.

Absorption spectra of the pigments prepared during this study are given in the annexed Table. Previous data on bacteriochlorophyll derivatives have been recorded by Pruckner *et al.*[11,18] and by Weigl.[19] The band at *ca.* 750 mμ appears to be characteristic of bacteriochlorophyll derivatives; it is shifted bathochromically to 770 mμ by the introduction of magnesium, *i.e.*, in bacteriochlorophyll itself, and hypsochromically to 727 mμ on reduction of the acetyl group (cf. VII). Although a quantitative spectrum of bacteriochlorophyll was not obtained it is apparent from results during the isolation (see p. 1730) that the ε value of the 770 mμ band in methanol must be considerably less than that reported for solutions in ether.[19,20]

*Light absorption data* (λ *in* mμ).

| λ | ε | λ | ε | λ | ε | λ | ε | λ | ε |
|---|---|---|---|---|---|---|---|---|---|
| Bacteriophæophytin (II; R = phytyl) In dioxan | | Bacteriomethylphæophorbid (II; R = Me) In dioxan | | Bacteriochlorin $e_6$ (III) In dioxan | | $Me_2$ ester In $C_6H_6$ | | 2-Acetylchlorin $e_6$ $Me_2$ ester (IV) In $C_6H_6$ | |
| 297 | 39,800 | 298 | 18,200 | 358 | 112,000 | 307 | 46,800 | 411 | 105,000 |
| 359 | 107,000 | 360 | 112,000 | 385 | 79,400 | 359 | 138,000 | 507 | 10,600 |
| 387 | 57,500 | 385 | 57,500 | 456 | 3,470 | 387 | 112,000 | 542 | 8,080 |
| 496 | 6,200 | 496 | 6,030 | 493 | 5,250 | 457 | 3,470 | 626 | 4,360 |
| 530 | 29,500 | 530 | 27,500 | 522 | 29,500 | 493 | 5,010 | 682 | 50,400 |
| 627 | 3,500 | 625 | 3,710 | 627 | 2,190 | 525 | 27,500 | | |
| 682 | 10,000 | 682 | 10,200 | 688 | 7,760 | 631 | 3,720 | | |
| 751 | 70,800 | 752 | 72,400 | 750 | 93,300 | 691 | 7,240 | | |
| | | | | | | 754 | 93,300 | | |
| Cu deriv. of (IV) In $C_6H_6$ | | Oxochloroporphyrin $e_6$ $Me_2$ ester (X *) In dioxan | | Cu deriv. of (X) In $C_6H_6$ | | Ester (VII) In $C_6H_6$ | | *b*-Octaethyltetrahydroporphin (VIII) In $C_6H_6$ | |
| 423 | 73,000 | 348 | 22,400 | 419 | 198,000 | 379 | 67,100 | 374 | 180,000 |
| 511 | 3,750 | 413 | 224,000 | 550 | 7,600 | 448 | 2,390 | 434 | 9,200 |
| 556 | 3,010 | 516 | 9,330 | 601 | 15,700 | 477 | 3,860 | 463 | 20,300 |
| 658 | 43,500 | 559 | 12,000 | | | 506 | 20,100 | 491 | 49,300 |
| | | 587 | 7,760 | | | 613 | 1,930 | 604 | 2,500 |
| | | 642 | 1,990 | | | 665 | 6,710 | 662 | 6,200 |
| | | | | | | 691 | 6,820 | 685 | 14,100 |
| | | | | | | 727 | 61,200 | 721 | 150,000 |

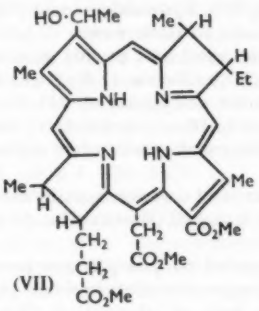
* = IV without the " extra " hydrogen atoms.

An additional characteristic of the bacterio-derivatives is the double Soret band at 360 and 385 mμ; the acetyl group appears to be necessary for this feature, as it is not shown by compounds (VII) or (VIII).

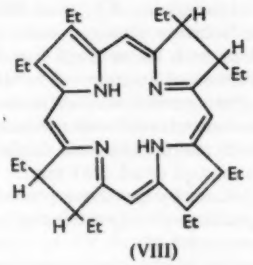
[18] Pruckner, *Z. phys. Chem.*, 1940, **187**, *A*, 257.
[19] Weigl, *J. Amer. Chem. Soc.*, 1953, **75**, 999.
[20] Holt and Jacobs, *Amer. J. Bot.*, 1954, **11**, 718.

For comparison with Eisner's synthetic *b*-octaethyltetrahydroporphin [8] (VIII) the ester (VII) was prepared by reduction of the bacteriochlorin (III) with borohydride. This compound could not be obtained crystalline, possibly because it was a mixture of epimers, and consequently only approximate ε values can be quoted.

*Infrared Spectra.*—The infrared spectra of macrocyclic pigments have not been studied




(VII)




(VIII)

in great detail. The most extensive work is that of Falk and Willis [21] on a series of porphyrins and hæms and of Thomas and Martell [22] on *mes o*-tetraphenylporphins. Apart from a few early results by Pruckner [18] of limited range, the only bacteriochlorophyll derivative studied is the parent pigment.[23]

For the pigments described in this paper, the N–H stretching band is a weak band at 3290—3240 cm.$^{-1}$, better observed in solution spectra (in $CHCl_3$); it is absent in the metallo-derivatives. The conjugated ester band (1720—1705 cm.$^{-1}$) attributable to the 6-methoxycarbonyl group in the esters (III) and (IV) is resolved from the normal ester band (1730 cm.$^{-1}$) in the KBr disc spectra but not in solution spectra ($CHCl_3$). In derivatives (II; R = phytyl and Me) containing the keto-group in a five-membered ring the above conjugated-ester band is replaced by one at 1690 cm.$^{-1}$. A band at 1665—1655 cm.$^{-1}$ appears to be diagnostic of the conjugated 2-acetyl group; in the ester (VII) this band is absent. These band assignments indicate that the carbonyl groups at positions 2 and 6 in bacteriochlorophyll must be conjugated with a π-electron system. This is in agreement with the assignment of the two " extra " hydrogen atoms to positions 3 and 4.

A band at 1618—1616 cm.$^{-1}$ appears in all the chlorophyll and bacteriochlorophyll derivatives examined but is absent in the porphins. Bacteriochlorophyll derivatives appear to be characterised by a series of intense bands in the 1000—800 cm.$^{-1}$ region; the chlorophylls and porphyrins only showed relatively weak absorption in this region.

## Experimental

Unless otherwise stated, alumina for chromatography is Peter Spence's Grade " H " alumina deactivated and neutralised by addition of 5 c.c. of 10% acetic acid per 100 g. of alumina. M. p. marked (K) were determined on a Kofler block. The solvent mixture used for paper chromatography was ethanol–water–ammonia (*d* 0·88) (80 : 15 : 5).

Infrared measurements were made by Mr. R. L. Erskine using a Grubb-Parsons double-beam instrument. Elementary analyses were carried out in the Micro-analytical Laboratory (Miss J. Cuckney) of Imperial College.

*Extraction of Bacteriophæophytin* (II; R = phytyl).—Bacteria (314 g.; *Chromatium* sp., El Agheila) were ground with methanol (500 c.c.) and then centrifuged. The colourless supernatant liquid was discarded; the deposit was ground with fresh methanol (500 c.c.) and re-centrifuged. The dark green supernatant liquid was collected and the deposit repeatedly re-extracted

[21] Falk and Willis, *Austral. J. Sci.*, 1951, **4**, *A*, 579.
[22] Thomas and Martell, *J. Amer. Chem. Soc.*, 1956, **78**, 1338.
[23] Weigl and Livingston, *ibid.*, 1953, **75**, 2173.

in this way until the extracts were pale yellow. The combined extracts were filtered through a fine sintered-glass filter to remove suspended particles, and gave *ca.* 2·5 l. of solution. Spectroscopic estimation of the bacteriochlorophyll content, using the absorption at 770 mμ and Holt and Jacobs's *E* value,[20] gave a value of 439 mg.

The methanolic solution was divided into 500 c.c. portions. Each was diluted with ether (500 c.c.), water (1 l.) added with swirling, and the colourless aqueous layer discarded. The combined ethereal layers (*ca.* 1 l.) were shaken with 22% hydrochloric acid (75 c.c.) to remove magnesium: the solution changed from bright green to dark violet. The ether layer was thoroughly washed with water until free from acid; emulsions at this stage were broken by the cautious addition of acetone. The dried ($Na_2SO_4$) solution (1·6 l.) was filtered and the bacteriophæophytin content was estimated, from the absorption at 747 mμ, to be 657 mg. The solution was concentrated under reduced pressure to 10 c.c., cooled to 0°, and filtered. The bacteriophæophytin (containing some sulphur and carotenoids) was washed with a little ether and then with methanol and dried (983 mg.).

In several isolations by the above procedure the ratio of spectroscopically estimated bacteriophæophytin to spectroscopically estimated bacteriochlorophyll (Holt and Jacobs's *E*) was between 1·54 and 1·75 (average 1·65).

A small quantity of the above material was purified by precipitation from the minimum of acetone with excess of hot methanol. Three-fold repetition of this process yielded chromatographically homogeneous bacteriophæophytin, m. p. 203° (K) (Found: C, 73·9; H, 8·7. Calc. for $C_{55}H_{74}O_6N_4$: C, 74·3; H, 8·6%).

*Bacteriomethylphæophorbid* (II; R = Me).—This material, prepared by Fischer and Hasenkamp's method [13] from bacteriophæophytin by ester exchange with methanolic hydrogen chloride, crystallised when the reaction mixture was cooled; the average yield from crude bacteriophæophytin was 78%, of material of m. p. 225—230° (K). A portion was purified by chromatography on alumina and crystallised from acetone–methanol as dark blue rhombs, m. p. 233—235° (K) (Found: C, 69·1; H, 7·0, 7·1; N, 9·0. Calc. for $C_{36}H_{40}O_6N_4$: C, 69·2; H, 6·45; N, 9·0%).

*Bacteriochlorin $e_6$ Trimethyl Ester* (III).—This was prepared [13] by methanolysis of bacteriomethylphæophorbid with diazomethane–methanol in the presence of pyridine, and purified by chromatography on alumina and elution with benzene–ether (4 : 1). Crystallisation from acetone–methanol gave steely-black needles (70%), m. p. 208—210° (K) (Found: C, 68·0; H, 7·35, 7·4; N, 8·4. Calc. for $C_{37}H_{44}O_7N_4$: C, 67·7; H, 6·75; N, 8·5%).

*2-Acetylchlorin $e_6$ Trimethyl Ester* (IV).—(*a*) Nitrogen was bubbled through a solution of bacteriochlorin $e_6$ trimethyl ester (20 mg.) in dry benzene (10 c.c.), 2 : 3-dichloro-5 : 6-dicyanobenzoquinone (7·3 mg., 1·05 mol.) in dry benzene (10 c.c.) was added, and the whole set aside at 20° for 30 min. in the dark. The pigment was then absorbed on a column of alumina. Elution with benzene–ether (9 : 1) afforded 2-acetylchlorin $e_6$ as a narrow dark brown band, followed by a trace of oxochloroporphyrin $e_6$ trimethyl ester as a pale blue zone. Evaporation of the brown solution and crystallisation of the residue from acetone–methanol gave 2-acetylchlorin $e_6$ (19 mg., 95%) as dark brown crystals with a blue metallic lustre, m. p. 245—250° (K) (Found: C, 68·0; H, 6·7; N, 8·4. Calc. for $C_{37}H_{42}O_7N_4$: C, 67·9; H, 6·5; N, 8·6%).

(*b*) 1 c.c. portions of a benzene solution of bacteriochlorin $e_6$ trimethyl ester (341 mg./l.) were mixed severally with 0·40 c.c. and 0·80 c.c. (0·5 and 1·0 mol.) of a solution (162 mg./l.) of 2 : 3-dichloro-5 : 6-dicyanobenzoquinone, and the mixtures were made up to 10 c.c. After 20 min. at 20° the intensities of absorption in the 755 and the 682 mμ region were measured, after appropriate dilution, and the concentrations of starting material and product estimated:

| Quinone added (mol.) | Bacteriochlorin unchanged (%) | Acetylchlorin formed (%) |
|---|---|---|
| 0·5 | 4·9 | 48 |
| 1·0 | 0 | 93 |

*Oxochloroporphyrin $e_6$ Trimethyl Ester* (IV minus 2H).—2-Acetylchlorin $e_6$ trimethyl ester (20 mg.) in dry benzene (10 c.c.) was heated under reflux in nitrogen with 2 : 3-dichloro-5 : 6-dicyanobenzoquinone (35 mg., 5 mol.) during 30 min. Chromatography on alumina and elution with benzene–ether (9 : 1) gave a bright purple solution. Evaporation followed by crystallisation of the residue from chloroform–methanol gave blue prisms (16 mg., 80%), m. p. 270—272° (K) (Found: N, 8·5. Calc. for $C_{37}H_{40}O_7N_4$: N, 8·6%).

*Copper Derivative of Pigment* (IV).—2-Acetylchlorin $e_6$ trimethyl ester (100 mg.) was heated

in boiling benzene (30 c.c.) under nitrogen; cupric acetate (100 mg.) in hot methanol was added. After 2 min. the bright blue-green solution was cooled, washed with water, dried, and evaporated. The residue was chromatographed on alumina, elution with benzene–ether (8 : 2) giving the *copper derivative* of the pigment as a sharp green band. Crystallisation from chloroform–methanol afforded blue-green needles (108 mg., 98%) (Found: C, 61·9; H, 5·9; Cu, 9·0. $C_{37}H_{46}O_7N_4Cu$ requires C, 62·0; H, 5·6; Cu, 8·9%).

*Copper Derivative of Pigment* (X = IV minus 2H).—(*a*) The preceding copper derivative (50 mg.) in boiling dry benzene (20 c.c.) was heated under nitrogen with 2 : 3-dichloro-5 : 6-dicyanobenzoquinone (16 mg., 1 mol.) during 30 min. Purification was by chromatography on alumina; the pigment was eluted as a green band with benzene–chloroform (4 : 1). Solutions in benzene and chloroform are dark red in fairly concentrated and blue-green in dilute solution. Evaporation of the eluate followed by crystallisation from chloroform–methanol gave the *derivative* as dark-purple needles (45 mg., 90%) (Found: C, 61·9; H, 5·7; Cu, 9·0. $C_{37}H_{38}O_7N_4Cu$ requires C, 62·2; H, 5·4; Cu, 8·9%).

(*b*) 1 c.c. portions of a solution (491 mg./l.) of the copper derivative of (IV) were mixed severally with 0·23 and 0·46 c.c. (0·5 and 1·0 ml.) of a solution of 2 : 3-dichloro-5 : 6-dicyanobenzoquinone (325 mg./l.). The solutions were heated at 80° for 30 min., cooled, and diluted to 10 c.c. After appropriate dilution the intensities of absorption in the 658 mμ region (starting material) and the 550 and the 600 mμ region (product) were measured and the concentrations estimated:

| Quinone added (mol.) | Copper deriv. of (IV) | Copper deriv. of (X) (%) | |
|---|---|---|---|
| | | 602 mμ | 550 mμ |
| 0·5 | 50 | 44 | 40 |
| 1·0 | 5 | 88 | 90 |

(*c*) Oxochloroporphyrin $e_6$ trimethyl ester (10 mg.) was heated under nitrogen in boiling benzene (10 c.c.), and cupric acetate (20 mg.) in hot methanol was added. After 2 min. the red-green solution was cooled, washed with water, dried, and evaporated. The residue was chromatographed on alumina; elution with benzene–chloroform (4 : 1) gave the copper derivative (8 mg.), spectroscopically identical with that obtained as in (*a*) above.

*Oxidation of Bacteriochlorin $e_6$ Trimethyl Ester.*—The deep blue solution of bacteriochlorin $e_6$ trimethyl ester (500 mg.) in 50% sulphuric acid (40 c.c.) was treated with ice (30 g.), cooled to −12°, treated with chromium trioxide (2 g.) in water (15 c.c.) with stirring during 1 hr., stirred for a further 4 hr. at −12°, allowed to reach room temperature, and then continuously extracted with ether for 48 hr. Evaporation of the extract afforded a yellow oil whose solution in water (10 c.c.) was adjusted to pH 10 (NaOH) and continuously extracted with ether for a further 48 hr., giving a neutral fraction (A). The aqueous layer was acidified to pH 3 with dilute hydrochloric acid and re-extracted with ether for 48 hr., giving an acid fraction (B).

Material from fraction (A), a yellow oil (44 mg.), was examined by paper chromatography, the spots being detected by an imide spray: $R_F$ 0·43 (faint) (dihydrohæmatinimide), 0·81—0·82 and 0·86—0·88 (ethylmethylsuccinimide and ethylmethylmaleimide). Authentic $R_F$ values with this solvent system [16] are: *cis*-dihydrohæmatinimide, 0·41; *trans*-dihydrohæmatinimide, 0·45; *cis*-ethylmethylsuccinimide, 0·79; *trans*-ethylmethylsuccinimide, 0·81; ethylmethylmaleimide, 0·87.

The infrared spectrum of the crude neutral fraction (A) in $CHCl_3$ included strong imide bands but no anhydride bands.

Hydrolysis of fraction (A) by concentrated hydrochloric acid (1 c.c.) under reflux for 1 hr. was followed by removal of the acid under reduced pressure, dissolution of the residue in water, and adjustment of the pH to 7 with sodium hydrogen carbonate. The solution was treated with neutral permanganate (30 mg. in 5 c.c. of water) and kept at 25° for 1 hr. After decolorisation with sulphur dioxide the solution was extracted with ether for 48 hr., giving a colourless oil which was examined by paper chromatography. Development with ethanolic bromocresol-green revealed two main spots: $R_F$ 0·14 (dihydrohæmatinic acid?) and 0·38 (ethylmethylsuccinic acid?). Authentic $R_F$ values are: *cisoid*-dihydrohæmatinic acid, 0·12; *transoid*-dihydrohæmatinic acid, 0·11; *cisoid*-ethylmethylsuccinic acid, 0·43; *transoid*-ethylmethylsuccinic acid, 0·40.

The oil was converted into the *p*-bromophenacyl ester in the usual way, the product being isolated with chloroform and chromatographed on alumina (neutralised with ethyl acetate).

The fractions eluted with benzene–light petroleum (3 : 2) afforded di-*p*-bromophenacyl *transoid*-ethylmethylsuccinate (24 mg., 6%), m. p. 112—113° (after two crystallisations from aqueous methanol), $[\alpha]_D^{24}$ −37°. The infrared spectrum (KBr disc) was identical with that of authentic racemic material.[16]

The acid fraction (B), a red-brown oil (200 mg.), was hydrolysed with concentrated hydrochloric acid and oxidised with neutral permanganate, as for (A), giving an acidic oil (131 mg.). Paper chromatography showed the presence of material of $R_F$ 0·14, corresponding to dihydrohæmatinic acid, as well as spots probably due to oxalic and succinic acids.

*Borohydride Reduction of Bacteriochlorin $e_8$ Trimethyl Ester.*—Bacteriochlorin $e_8$ trimethyl ester (20 mg.) in dioxan (5 c.c.) was treated with potassium borohydride (20 mg.) in 50% aqueous dioxan (50 c.c.) and set aside at 20° for 1 hr., the solution changing from olive-green with a violet tinge to bright green. Water was added and the pigment isolated with ether. Chromatography on alumina and elution with benzene–ether (9 : 1) gave a small quantity of starting material (4 mg.), followed by a bright green band which on evaporation gave a green uncrystallisable gum (13 mg.), whose infrared spectrum (in $CHCl_3$) indicated replacement of the acetyl group by hydroxyethyl, the ester groups being retained.

These investigations were made possible by the kindness and skilful collaboration of Dr. G. A. Miller and his colleagues of the Antibiotic Research Station, Clevedon, who made available the *Chromatium* bacteria used as a source of pigment; also by financial support from the Rockefeller Foundation whom we thank.

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## 356. 1 : 2-*Dicarboxylic Acids. Part IV.* The α-Ethyl-α′-methylsuccinic Acids and Their Derivatives.*

By J. H. Golden and R. P. Linstead.

The diastereoisomeric α-ethyl-α′-methylsuccinic acids and a number of their derivatives have been prepared for comparison with compounds obtained by the oxidation of derivatives of bacteriochlorophyll (preceding paper). Chromatographic behaviour and infrared spectra are recorded, and stereochemical configurations are assigned.

The oxidation of bacteriochlorophyll derivatives has been postulated to yield substances derived from α-ethyl-α′-methylsuccinic acid and this has now been proved to be the case (Golden, Linstead, and Whitham[1]). This prompted the re-investigation of the two diastereoisomeric forms of this acid, which is described in the present paper.

The succinic acid can exist in the diastereoisomeric forms (I and II). Both of these give rise to anhydrides (III and (IV) and similar heterocyclic derivatives. The nomenclature is that used for the dihydrohæmatinic acids:[2] the classical terms *cis* and *trans* of the cyclic systems lead to the terms *cisoid* and *transoid* for the corresponding acids. As shown below, the *cis–cisoid*-series correspond to the higher-melting acid, which has been called " fumaroid " or " mesoid " by previous workers. The lower-melting *transoid*-acid has previously been called " maleinoid," " racemoid," or " DL." These earlier terms are best avoided. Both acids have been partially resolved by Berner and Leonardsen.[3]

The two diastereoisomerides, first prepared by Zelinsky[4] and Bischoff[5] and their collaborators, were thoroughly examined by von Auwers.[6] We prepared a mixture of

* Part III, *J.*, 1954, 3730.

[1] Golden, Linstead, and Whitham, preceding paper.
[2] Ficken, Johns, and Linstead, *J.*, 1956, 2280.
[3] Berner and Leonardsen, *Annalen*, 1939, **538**, 1.
[4] Zelinsky and Bitschichin, *Chem. Zentr.*, 1890, **11**, 43.
[5] Bischoff *et al.*, *Ber.*, 1889, **22**, 1817; 1890, **23**, 647; 1891, **24**, 1066.
[6] (*a*) von Auwers, *Annalen*, 1896, **292**, 132, 152; (*b*) von Auwers and Fritzweiler, *ibid.*, 1897, **298**, 147.

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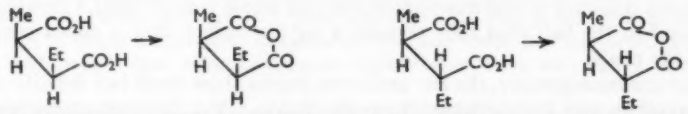
them by the hydrolysis of ethyl αβ-dicyano-α-ethylbutyrate.[7] The higher-melting (*cisoid*) acid was obtained by crystallisation and the residual mixed acids were converted into the mixed ammonium salts. Distillation then gave the *trans*-imide, which could be converted into the parent, low-melting acid by rapid hydrolysis with mineral acid. The melting




(I) *cisoid*-acid (III) *cis*-anhydride (II) *transoid*-acid (IV) *trans*-anhydride

points of the acids agreed with those recorded by von Auwers and the infrared spectra with those recorded by Schotte [8] (see Table).

The *trans*-anhydride was obtained by treatment of the mixed acids with thionyl chloride followed by distillation; it yielded *transoid*-acid on hydrolysis. The *cis*-anhydride, which is easily inverted, was obtained by the method successful for *cis*(" *ms* ")-dimethylsuccinic anhydride, namely, treatment of the disodium salt of the acid with thionyl chloride in dry ether.[9] The *cis*-anhydride distilled unchanged under $10^{-6}$ mm. and on hydrolysis gave the *cisoid*-acid. The early report by Zelinsky and Bitschichin [4] that only one anhydride exists is incorrect, as already shown by von Auwers and Fritzweiler.[6b]

The ethylmethylsuccinimides, of special importance in relation to bacteriochlorophyll degradation, have not previously been described. It has been reported [6b] that the same *N*-phenylimide and *N*-tolylimide were obtained from both acids. The stable *trans*-imide, m. p. 61°, was readily obtained by dry distillation of the ammonium salts of either the *transoid*-acid or the mixed acids. The labile *cis*-imide was obtained by the method established by Linstead and Whalley [9] in the dimethyl series, catalytic hydrogenation of the corresponding maleimide. The *cis*-imide, m. p. 51°, sharply depressed the m. p. of its *trans*-isomeride. It differed markedly from it in infrared spectrum, and on hydrolysis gave the *cisoid*-acid. Table 1 summarises the properties of the two acids and their derivatives.

TABLE 1. *α-Ethyl-α'-methylsuccinic acids and their derivatives.*

| | *cis-cisoid*-Series | | *trans–transoid*-Series | |
|---|---|---|---|---|
| | Present work | Lit. | Present work | Lit. |
| Acid ..... | M. p. 182° | 180—182° (ref. 6*b*) | M. p. 102° | 101—102° (ref. 6*b*) |
| Anhydride ..... | B. p. 60°/$10^{-6}$ mm. | 118—119°/12 mm. (ref. 3) | B. p. 121°/15 mm. | 114—115°/12 mm. (ref. 3) |
| | $n_D^{21}$ 1·4482 | | $n_D^{21}$ 1·4459 | |
| Imide ..... | M. p. 51° | | M. p. 61—62° | |
| Di-*p*-bromophenacyl ester | M. p. 119° | | M. p. 122° | |

The configurations are assigned for three reasons. (i) The hydrogenation of methylethylmaleinimide may be presumed to give a *cis*-product, as in similar cases: this leads to a *cis*-configuration for the imide, m. p. 51°. (ii) Schotte [8] found, for a range of substituted succinic acids, that the lower-melting acid is *transoid* and has characteristic differences in the infrared spectrum, notably in the C=O stretching frequency which is a singlet for the *cisoid*- but a doublet for the *transoid*-form. On this basis our acid of m. p. 102° and its derivatives are *transoid*. (iii) The inversions of the heterocyclic derivatives reported below are parallel with those in the dimethylsuccinic series (where the configurations are certain) if the assignments given in Table 1 are correct.

The inversions of configurations are summarised in Table 2 and described in the Experimental section.

[7] Braun, Keller, and Weissbach, *Annalen*, 1931, **490**, 179.
[8] Schotte, *Arkiv Kemi*, 1956, **9**, 397; cf. Schotte and Rosenberg, *ibid.*, 1954, **7**, 479; 1955, **8**, 16.
[9] Linstead and Whalley, *J.*, 1954, 3722.

TABLE 2.

| | | |
|---|---|---|
| Acids ..... | Water or mineral acid at 180° | *cisoid* / *transoid* ⟶ Mixture |
| Anhydride [44] ..... | Heat | *cis* ⟶ *trans* |
| Imide ..... | Heat, urea fusion | *cis* ⟶ *trans* |

The greater stability of the *trans*-anhydride and imide is attributed, following Linstead and Whalley,[9] to the fact that they contain a zig-zag rather than a coiled conformation of the paraffin chain.

On paper chromotography, the *cis*- and *trans*-imides show small but definite differences from one another and from ethylmethylmaleinimide. The difference between the two acids on paper chromatograms is also small, but the two acids react differently with the indicator and are easily distinguished. Chromatographic separations of ethylmethylsuccinic acids from dihydrohæmatinic acids were easily effected both on paper and on silica gel.

The infrared spectra of the acids, di-*p*-bromophenacyl esters, anhydrides, and imides of the two series are recorded and discussed in the Experimental section. We also record the preparation of *cisoid*-α-ethyl-α′-methylsuccinamide and of the methyl ester of *trans*-dihydrohæmatinic imide (required for chromatographic experiments).

## EXPERIMENTAL

Microanalyses by Miss J. Cuckney; infrared measurements by Mr. R. L. Erskine of this Department. Alumina for chromatography unless otherwise stated was Savory and Moore's, deactivated with water to Brockmann grade IV.

*Preparation of α-Ethyl-α′-methylsuccinic Acids and their Derivatives.*—Ethyl αβ-dicyano-α-ethylbutyrate, prepared [7] in 51% yield, had b. p. 198°/60 mm., $n_D^{25}$ 1·4379. The ester (100 g.) was refluxed for 24 hr. with concentrated hydrochloric acid (600 c.c.). The clear solution was cooled at 0° overnight, then filtered from deposited solid, which was washed with 50% hydrochloric acid (20 c.c.) and recrystallised from water (yield, 19 g.; 23%; m. p. 182°). Recrystallisation from water or xylene gave needles of *cisoid*-ethylmethylsuccinic acid, m. p. 182°.

The aqueous liquors were extracted with ether for 24 hr. and the extract dried and concentrated, to give oily mixed acids (62·5 g., 76%). These (44·7 g.) were treated with aqueous ammonia (75 ml.; *d* 0·88) and left overnight. Distillation gave an aqueous solution of the *trans*-imide, which was extracted with ether for 24 hr. The extract was dried and concentrated, to give crude *trans*-imide (31·1 g., 79%). The imide partially solidified at 0° and was drained on a porous tile, leaving a white solid (16·9 g.), m. p. 49°. Sublimation and recrystallisation from water and light petroleum (b. p. 40—60°) gave pure trans-*α-ethyl-α′-methylsuccinimide*, m. p. 61—62° (Found: C, 59·8; H, 7·5; N, 9·9. $C_7H_{11}O_2N$ requires C, 59·85; H, 7·05; N, 10·2%). The infrared absorption and m. p. of this sample were identical with those of material prepared in the same manner from pure *transoid*-ethylmethylsuccinic acid.

*trans*-Ethylmethylsuccinimide (5 g.) was refluxed with concentrated hydrochloric acid (25 c.c.) for 3·5 hr., then cooled and extracted with ether. Concentration of the dried extract yielded a gum which crystallised on addition of water, to give a white solid (4·5 g., 79%), m. p. 99°. Extractive crystallisation from light petroleum (b. p. 40—60°) yielded pure *transoid*-ethylmethylsuccinic acid, m. p. 102°.

trans-*Anhydride*. Mixed ethylmethylsuccinic acids (17·8 g.) were refluxed for 90 min. with acetyl chloride (25 c.c.). Excess of acetyl chloride was removed and the residue distilled, giving a colourless liquid (13·8 g., 85·5%). Redistillation yielded the pure *trans*-ethylmethylsuccinic anhydride, b. p. 121°/15 mm., $n_D^{21}$ 1·4459 (Found: C, 59·5; H, 6·8. Calc. for $C_7H_{10}O_3$: C, 59·1; H, 7·1%).

Hydrolysis of the anhydride (0·663 g.) with boiling water (0·5 c.c.) for 20 min. yielded (after ether-extraction) *transoid*-ethylmethylsuccinic acid (731 mg., 99%), m. p. 85° raised to 98° by extraction with light petroleum (b. p. 40—60°).

cis-*Anhydride*. A suspension of the finely ground, dry sodium salt, formed from the *cisoid*-acid (10 g.), in dry ether (100 c.c.), was treated with redistilled thionyl chloride (5 c.c.) in ether (20 c.c.) during 10 min. The mixture was left at room temperature for 12 hr., then filtered,

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and the solid washed with anhydrous ether. The filtrate was evaporated, which left a colourless liquid (7·84 g., 86%). This, on distillation at 60/$10^{-6}$ mm., yielded pure *cis*-ethylmethylsuccinic anhydride, $n_D^{21}$ 1·4482 (Found: C, 58·9; H, 7·2%).

Hydrolysis of the anhydride (243 mg.) with boiling water (0·5 c.c.) for 10 min. yielded (after ether-extraction) *cisoid*-ethylmethylsuccinic acid (257 mg., 95%), m. p. and mixed m. p. 179°.

*Ethylmethylmaleinimide.*—Ethyl α-ethylacetoacetate, b. p. 97°/18 mm., $n_D^{19}$ 1·4235, was prepared from ethyl acetoacetate in 79% yield, converted into the cyanohydrin, hydrolysed, and dehydrated [10] to ethylmethylmaleic anhydride. The anhydride was converted into the imide by fusion with urea,[10] then sublimation and crystallisation from water gave the pure imide, m. p. 68°.

cis-*Ethylmethylsuccinimide.*—Pure ethylmethylmaleimide (996 mg.) in purified ethyl acetate (25 c.c.) was hydrogenated at atmospheric pressure in the presence of Adams catalyst (27 mg.) (uptake, 1 mol., complete in 5 hr.). Filtration and concentration yielded a solid, m. p. 50° (1·014 g., quantitative yield). Recrystallisation from light petroleum (b. p. 40—60°) gave leaflets, m. p. 51°, of cis-*α-ethyl-α-methylsuccinimide* (Found: C, 59·7; H, 7·6; N, 10·1. $C_7H_{11}O_2N$ requires C, 59·55; H, 7·85; N, 9·9%), mixed m. p. with the *trans*-imide 35°.

The *cis*-imide (63·1 mg.) was refluxed with concentrated hydrochloric acid (1 c.c.) for 1 hr. The cold solution was extracted with ether for 24 hr. The dried extract was concentrated, to yield *cisoid*-acid (71·3 mg., 99%), m. p. and mixed m. p. 176°.

p-*Bromophenacyl Esters.*—(*a*) To the *cisoid*-acid (250 mg.), dissolved in the minimum amount of 2N-sodium hydroxide and rendered just acid with 2N-hydrochloric acid, was added *p*-bromophenacyl bromide (870 mg.) in ethanol (7 c.c.). The solution was refluxed for 2 hr., then cooled; a white solid (814 mg., 94%), m. p. 119°, crystallised and was washed with water. Recrystallisation from ethanol gave the *di-p-bromophenacyl derivative* as needles, m. p. 119° (Found: C, 50·1; H, 4·3; Br, 28·9. $C_{22}H_{22}O_6Br_2$ requires C, 49·8; H, 4·0; Br, 28·8%).

(*b*) By the foregoing procedure the *transoid*-acid (250 mg.) yielded the corresponding di-*p*-bromophenacyl derivative (836 mg., 97%), m. p. 100°. Recrystallisation from methanol yielded needles of the *ester*, m. p. 122° (depressed to 106° on admixture with the *cisoid*-ester) (Found: C, 49·85; H, 4·2%).

The *S*-benzyl*iso*thiuronium, benzylamine, and piperidine salts of the ethylmethylsuccinic acids were too soluble for convenient preparation.

*Conversion of* cis-*Ethylmethylsuccinimide into the* trans-*Isomer.*—*cis*-Imide (300 mg.), mixed with urea (230 mg.), was kept at 155—165° for 3·5 hr. After cooling, the solid was dissolved in water and extracted with ether for 24 hr. The ethereal solution was filtered from urea, dried ($Na_2SO_4$), and evaporated, yielding white crystals (304 mg.), m. p. 51—52°. Sublimation yielded crystals (249 mg.), m. p. 53°, having infrared absorption identical with that of the *trans*-imide. Recrystallisation from light petroleum raised the m. p. to 60—61°.

*Melting points of Mixtures of* cisoid- *and* transoid-*Ethylmethylsuccinic Acids.*—Mixtures of the acids were prepared and their m. p. determined on an electric m. p. apparatus. The *cisoid*-acid was only slightly soluble in the acid melts.

| *cisoid* (%) ..... | 0 | 11 | 28 | 36·5 | 46 | 56 | 64 | 73 | 82 | 90 | 95 | 100 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| M. p. ..... | 102° | 98° | 97° | 95—96° | 98° | 100° | 104° | 124° | 135° | 157° | 169° | 182° |

*Interconversion of* cisoid- *and* transoid-*Ethylmethylsuccinic Acids.*—Samples of *cisoid*- and *transoid*-acids (50 mg.) were heated (*a*) alone, (*b*) with water (2 c.c.), and (*c*) with concentrated hydrochloric acid (2 c.c.) at 180° for 72 hr. The products were evaporated to dryness over potassium hydroxide in a desiccator and their identity determined by paper chromatography and m. p.

(*a*) *cisoid*: Unchanged, m. p. 182°.

*transoid*: Gave a mixture of *cisoid*- and *transoid*-material; m. p. 71°. This on treatment with water (2 c.c.) and evaporation at room temperature melted at 95—97°, unchanged by further treatment with water; hence >50% of *transoid*-form.

(*b*) The *cisoid*- and the *transoid*-form both gave material of m. p. about 110—115°; hence an equilibrium mixture containing 30—35% of the *transoid*-form.

(*c*) The *cisoid*- and the *transoid*-form both gave low-melting mixtures of *cisoid*- and *transoid*-material. On treatment with water, as in (*a*), the m. p.s were raised to 95—97°; hence >50% of *transoid* material.

[10] Muir and Neuberger, *Biochem. J.*, 1949, **45**, 164.

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The low-melting crude products obtained in some of these experiments probably contain anhydrides.

*Paper-chromatography of Acids and Imides.*—Solutions of the pure compounds (1% in methanol) were spotted on paper and developed (descending method) with ethanol–water–ammonia (*d* 0·88) (80 : 15 : 5). All compounds showed clearly defined spots with negligible tailing; $R_F$ ±0·02; relative values reproducible:

(a) *Imides*

Developed with *o*-tolidine by an adaptation of the method of Reindel and Hopper.[11]

| | $R_F$ |
|---|---|
| *cis*-Dihydrohæmatinimide | 0·41 |
| *trans*- ,, | 0·45 |
| *trans*-Dihydrohæmatinimide Me ester | 0·77 |
| *cis*-Ethylmethylsuccininimide | 0·79 |
| *trans*- ,, | 0·81 |
| Ethylmethylmaleinimide | 0·87 |
| Hæmatinimide | 0·51 |
| Benzylamine * | 0·82 |

* Benzylamine salts of, *e.g.*, dihydrohæmatinimide, give a double spot.

Mixtures of *cis*- and *trans*-isomers form a double spot but do not separate clearly.

(b) *Acids*

Developed with ethanolic bromocresol-green, followed by lead acetate.

| | $R_F$ |
|---|---|
| Oxalic | 0·00 |
| Succinic | 0·26 |
| Malonic | 0·17 |
| *transoid*-Ethylmethylsuccinic | 0·40 |
| *cisoid*- ,, | 0·43 |
| Ethylmethylmaleic † | 0·56 |
| *cisoid*-Dihydrohæmatinic | 0·12 |
| *transoid*- ,, | 0·11 |

† Anhydride dissolved in aqueous-methanolic ammonia.

The acids were also detectable by the imide spray (cf. *a*). *cis*- and *trans*-Isomers did not separate clearly, but the ethylmethylsuccinic acids were distinguishable by difference in the colour when freshly sprayed.

*Partition Chromatography of* cisoid-*Ethylmethylsuccinic and* cisoid-*Dihydrohæmatinic Acid.*—The acids (25 mg. of each) were dissolved together in ether saturated with water (5 c.c.) and chromatographed on silica gel saturated with water (20 × 1·5 cm.). The column was eluted with ether saturated with water, 3 ml. fractions being collected and identified by paper chromatography.

Fractions 1—2: nil. 3—6: *cisoid*-ethylmethylsuccinic acid (19·7 mg., 79%), m. p. 179°. 7—8: mixed acids (9·5 mg.). 9—20: *cisoid*-dihydrohæmatinic acid (11·8 mg., 47%), m. p. 180°. 21—40: traces only of acids. The total recovery was 82%. Addition of methanol failed to remove further acid. Use of ethyl acetate saturated with water, instead of ether, gave comparable results; benzene was ineffective.

*Infrared Absorption of Ethylmethylsuccinic Derivatives.*—(a) *Acids.* The *cisoid*- and the *transoid*-acid and their *p*-bromophenacyl esters gave characteristic curves and were readily distinguishable. Frequencies (cm.$^{-1}$) (in Nujol mulls) are tabulated (cf. Schotte [8]).

| Acids | | | *p*-Bromophenacyl esters | |
|---|---|---|---|---|
| *cisoid* | *transoid* | Assignment | *cisoid* | *transoid* |
| 1692 s | 1715 s<br>1698 s | C=O stretching | 1734 s | 1745 s, 1736 s |
| 1282 ms | Series | C=O stretching of carbonyl | 1703 s | 1706 s, 1694 s |
| 952 m | 937 m<br>897 m | OH out-of-plane bending | 1586 ms | 1587 s, 1570 w |

(b) *Anhydrides.* The spectra of the ethylmethylsuccinic anhydrides showed marked differences, especially in the 7—9·5 and 12—14 μ regions. The C=O vibration frequencies (obtained in a liquid film) are tabulated; the values are typical for a five-membered anhydride ring (cf. ref. 12).

| | *cis* | *trans* | Succinic anhydride [12] | Assignment |
|---|---|---|---|---|
| | 1850 | 1853 | 1865 | C=O vibration |
| | 1777 | 1779 | 1782 | |
| $\Delta\nu$ | 73 | 74 | 83 | |

(c) *Imides.* The imides possessed characteristic curves and were readily distinguishable from each other and from ethylmethylmaleinimide. The succinimides possessed a characteristic

[11] Reindel and Hopper, *Chem. Ber.*, 1954, **87**, 1103.
[12] Bellamy, "Infra-red Spectra of Complex Molecules," Methuen, London, 1954.
[13] Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," Van Nostrand, New York, 1949.

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band (*ca.* 1200 cm.$^{-1}$) not shown by the corresponding maleinimide. Frequencies (cm.$^{-1}$) in Nujol mulls are tabulated.

| Ethylmethylmaleinimide | Ethylmethylsuccinimide cis | Ethylmethylsuccinimide trans | Assignment |
|---|---|---|---|
| 3185 m | 3165 m | 3145 m | NH stretching |
| 3012 m | 3049 m | 3040 m | |
| 1764 s | 1776 m | 1770 m | Imide bands |
| 1709 s | 1698 s | 1692 s | |
| — | 1195 s | 1185 s | Succinimide band |

trans-*Dihydrohæmatinimide Methyl Ester.*—*trans*-Dihydrohæmatinimide (502 mg.) in ether (50 c.c.) was treated with excess of diazomethane in ether (50 c.c.). After 10 min. excess of diazomethane and ether were removed and the residue (534 mg., 99%) was transferred to a bulb tube. The clear oil was distilled, giving the *methyl ester*, b. p. 150°/0·5 mm., $n_D^{18}$ 1·4910 (Found: C, 54·6; H, 6·6; N, 7·1. $C_9H_{13}O_4N$ requires C, 54·3; H, 6·6; N, 7·0%).

cisoid-α-*Ethyl-α′-methylsuccinamide* [with P. Walker].—The *cis*-imide (200 mg.) was dissolved in 1 c.c. of aqueous ammonia (*d* 0·88) and kept at 0° for 2 days. The white crystals which separated were washed with water and with methanol. Recrystallisation from aqueous ammonia gave the cisoid-*amide* (40%), m. p. 340—342° (Found: N, 17·8. $C_7H_{14}O_2N_2$ requires N, 17·8%). Hydrolysis gave the *cisoid*-acid.

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[*Received, November 27th*, 1957.]

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## 357. *Homologous 9-Anthryl-1′-naphthylalkanes and a New Carbon–Carbon Cleavage occurring during Reduction by Lithium Aluminium Hydride.*

By Peter Rona and Uri Feldman.

The first three homologous 9-anthryl-1′-naphthylalkanes (I; $n$ = 1—3) have been synthesised. Reduction of 9-1′-naphthoylanthracene and 9-benzoylanthracene by lithium aluminium hydride affords 9-anthryl-1′-naphthylmethane and 9-benzylanthracene, respectively, but the hydrogenolysis in each case is accompanied by another reaction involving cleavage of a carbon–carbon single bond. Thus, anthracene is formed in each case, accompanied by 1-naphthylmethanol and benzyl alcohol, respectively.

It was thought by Dr. O. Schnepp, of this Department, that in certain compounds containing aromatic nuclei separated by a chain of insulating (saturated) carbon atoms, a new type of energy transfer from one aromatic nucleus to the other should be observable. After the synthesis of the compounds reported in this communication, this expectation was indeed realised.[1]

Homologous compounds of structure (I) have been prepared. Friedel–Crafts reaction of 1-naphthoyl chloride with anthracene in nitrobenzene in the absence of catalyst afforded 9-1′-naphthoylanthracene, in analogy to the reaction of benzoyl chloride with anthracene.[2] Although Huang-Minlon reduction or catalytic hydrogenolysis of this ketone was unsuccessful, reduction of the ketone by lithium aluminium hydride afforded the desired

1-$C_{10}H_7$·[$CH_2$]$_n$·$C_{14}H_9$-9 (Ia, $n$ = 1; Ib, $n$ = 2; Ic, $n$ = 3)

9-anthryl-1′-naphthylmethane (I*a*), in 17% yield after chromatography of the reduction mixture. From the portion of the product which did not give the desired product (I*a*), anthracene was isolated in 65% yield and 1-naphthylmethanol in 51% yield; these results

* *Note added March 6th*, 1958.—Dornow and Furst (*Chem. Ber.*, 1957, **90**, 1774) reported a carbon–carbon cleavage under similar reduction conditions.

[1] Schnepp, *J. Chem. Phys.*, in the press.
[2] Nenitzescu, Isacescu, and Ionescu, *Annalen*, 1931, **491**, 210.

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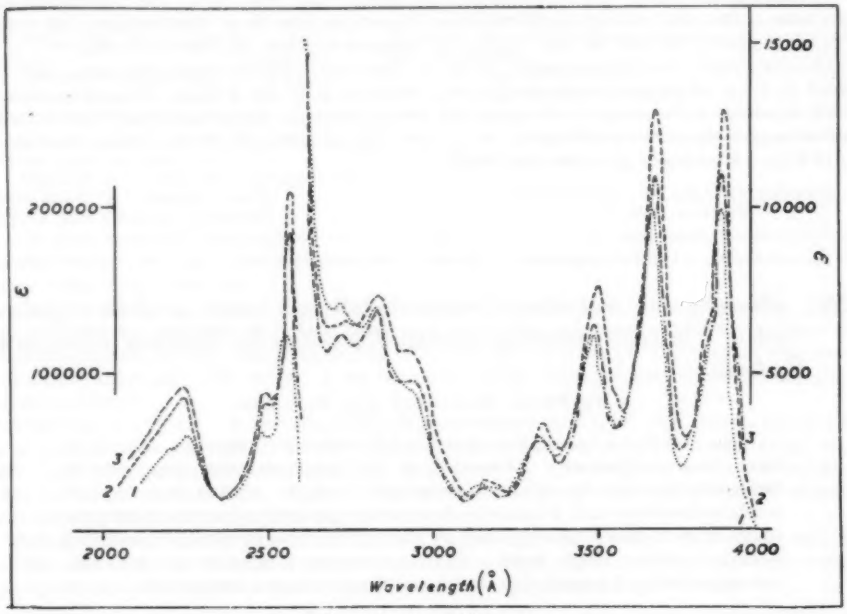
indicate that cleavage of a carbon–carbon single bond occurred during the reduction. Although cleavage of ether bonds [3] and deamination [4] are known in such reductions, we are unaware of such cleavages previously in the case of a C–C single bond.*

The possibility that the basic conditions prevailing during this reduction are responsible for the observed cleavage at the ketone stage, though improbable *a priori*, was ruled out by refluxing 9-1′-naphthoylanthracene alternatively with excess of lithium amide in tetrahydrofuran or with saturated ethanolic potassium hydroxide for 4·5 hr. The ketone was recovered unchanged in each case, practically quantitatively.

9-Benzoylanthracene [2] was prepared and reduced with lithium aluminium hydride. It afforded 9-benzylanthracene [5] in 24% yield but this was again accompanied by




All spectra in *cyclo*hexane.

Curve 1, compound I*a*; curve 2, compound I*b*; curve 3, compound I*c*.

anthracene and by benzyl alcohol. Again, in this case the ketone was quantitatively recovered after refluxing for 4·5 hr. under the above-mentioned basic treatments.

Several reasonable mechanisms can be envisaged for the observed carbon–carbon cleavage, taking into account various stages of the lithium aluminium hydride reduction process. The mechanistic problem and the scope of this apparently new type of cleavage are being studied further.

In order to prove the structure of 9-anthryl-1′-naphthylmethane it was prepared (45% yield) by an alternative route from 1-naphthylmethylmagnesium bromide and anthrone; the 2-9′-anthryl-1-1″-naphthylethane (I*b*) was prepared from 2-1′-naphthylethylmagnesium bromide and anthrone in 52% yield. 3-9′-Anthryl-1-1″-naphthylpropane (I*c*) was analogously prepared from 3-1′-naphthylpropylmagnesium bromide in 20% yield.

The ultraviolet absorption spectra of the above three hydrocarbons are given in the Figure.

[3] Freudenberg and Wilke, *Chem. Ber.*, 1952, **85**, 78.
[4] Adams and Moje, *J. Amer. Chem. Soc.*, 1952, **74**, 5557.
[5] E. Bergmann and Fujise, *Annalen*, 1930, **480**, 188.

## Experimental

*9-1'-Naphthoylanthracene.*—A mixture of 1-naphthoyl chloride (18·7 g.), anthracene (8 g.), and nitrobenzene (16 g.) was heated at 180°. After several minutes vigorous evolution of hydrogen chloride started. Heating at 180° was continued for 1·5 hr. Next morning the ketone which crystallised was filtered off. Recrystallisation from acetic acid afforded the ketone (11·2 g., 71%), m. p. 205—206°. Chromatography of a 2 g. sample of this ketone dissolved in benzene (30 ml.) on basic alumina (40 g.; Fisher) and elution with benzene–hexane (1 : 1) yielded traces of anthracene; further elution with chloroform afforded 1·8 g. of *ketone* which, when recrystallised from acetic acid, was slightly yellow; it had m. p. 211—213° (Found: C, 90·0; H, 5·2. $C_{25}H_{16}O$ requires C, 90·3; H, 4·85%); $\nu_{max.}$ (in $CHCl_3$) 1660 cm.$^{-1}$ (C=O).

*9-Anthryl-1'-naphthylmethane.*—(*a*) The above chromatographed ketone (1·5 g.), dissolved in dry tetrahydrofuran (40 ml.), was added dropwise to a suspension of lithium aluminium hydride (1 g.) in dry tetrahydrofuran (20 ml.). The mixture was refluxed for 3·5 hr. (after 2 hr. it became dark brown and exhibited strong fluorescence in ultraviolet light). After being kept overnight at room temperature, the mixture was treated with ethyl acetate, then with Rochelle salt solution, and the solvents were removed under reduced pressure. Water, benzene, and ether were added, and the organic layer was separated, extracted with saturated salt solution, and dried ($MgSO_4$). After removal of solvents the yellow crystalline residue was thrice recrystallised from *cyclo*hexane–benzene, affording anthracene, m. p. 212° (400 mg.), identical (infrared spectrum and mixed m. p.) with an authentic sample.

The mother-liquors were combined and the solvents removed. The residual yellow oil was dissolved in hexane (10 ml.) and chromatographed on basic alumina (15 g.; Fisher). Elution gave anthracene (60 mg.), followed by 9-anthryl-1'-naphthylmethane (250 mg., 17%), eluted by hexane–benzene (1 : 1), which exhibited blue fluorescence in ultraviolet light, and finally an oil (300 mg.) eluted by chloroform–benzene (3 : 1). The slightly yellow *hydrocarbon* had m. p. 182—184° (sintering at 180°) (from *cyclo*hexane) (Found: C, 93·8; H, 5·6. $C_{25}H_{18}$ requires C, 94·3; H, 5·7%).

The oil obtained from the last fractions of the above chromatographic column solidified after distillation (b. p. 95—105°/0·3 mm., m. p. 58—60°). It was identical (infrared spectrum and mixed m. p.) with authentic 1-naphthylmethanol.

(*b*) The Grignard reagent was prepared under nitrogen from 1-bromomethylnaphthalene [6] (2 g.) and magnesium (220 mg.) in dry ether (20 ml.). Anthrone (550 mg.) in dry benzene (15 ml.) was added dropwise with stirring. The mixture was left overnight, refluxed for a further hour, cooled, and decomposed with 3M-sulphuric acid (20 ml.). The usual working-up gave a yellow oil (1·8 g.). Its hexane solution was chromatographed on basic alumina (40 g.; Fisher). The following fractions were obtained: anthracene (30 mg.); 1 : 2-di-1'-naphthylethane (450 mg.), m. p. 164—165° (from *cyclo*hexane); [7] 9-anthryl-1'-naphthylmethane (460 mg., 45%), m. p. 186—187° (from *cyclo*hexane), identical with the substance prepared by method (*a*).

9-1'-Naphthoylanthracene (200 mg.) was refluxed for 4·5 hr. with lithium amide (250 mg.) in dry tetrahydrofuran (10 ml.). Another portion of the ketone (200 mg.) was refluxed for 4·5 hr. with saturated ethanolic potassium hydroxide (20 ml.). In both cases the ketone was recovered nearly quantitatively.

*9-Benzoylanthracene.*—A mixture of anthracene (8 g.), benzoyl chloride (12 g.), and nitrobenzene (16 g.) was heated under reflux for 3 hr. and kept overnight at room temperature. The solid which separated (2·6 g.) was filtered off, and the mother-liquor steam-distilled to remove nitrobenzene. The black residue was dissolved in glacial acetic acid and afforded more of the product (4·8 g.; total yield 58%), m. p. 148—153° (from acetic acid). Chromatography of a solution of this product (3 g.) in benzene (100 ml.) on basic alumina (90 g.; Fisher), followed by elution with benzene–hexane (1 : 1), afforded anthracene (150 mg.). Further elution with benzene–chloroform (1 : 1) gave the yellow ketone (2·2 g.), m. p. 148—149° (from acetic acid). Nenitzescu *et al.*[1] report m. p. 148°, $\nu_{max.}$ (in $CHCl_3$) 1667 cm.$^{-1}$ (C=O).

*9-Benzylanthracene.*—A solution of the above purified ketone (1·5 g.) in dry tetrahydrofuran (40 ml.) was added dropwise to a suspension of lithium aluminium hydride (850 mg.) in the same solvent (20 ml.), an immediate vigorous reaction setting in. The mixture was fluorescent in

[6] Catch and Evans, *J.*, 1957, 2797.
[7] Bamberger and Lodter, *Ber.*, 1888, **21**, 54.

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ultraviolet light whereas a solution of the starting material was not. Refluxing was continued for 4 hr., the mixture then being kept at room temperature for 36 hr. Working-up by the Rochelle salt procedure was followed by careful removal of the tetrahydrofuran through a 25 cm. Vigreux column so as to minimise loss of benzyl alcohol. The remaining solution was extracted with benzene, the extract dried ($Na_2SO_4$), and most of the benzene removed, again by careful distillation. The residual semicrystalline mass, not entirely free from benzene, was suspended in hexane (100 ml.) and applied to a column of basic alumina (30 g.; Fisher). Elution with hexane gave 9-benzylanthracene (360 mg., 24%), m. p. 130—132° (sinters at 127°) (from hexane) (Found: C, 93·85; H, 6·0. Calc. for $C_{21}H_{16}$: C, 94·0; H, 6·0%). Bergmann and Fujise [8] report m. p. 133°. Further elution with hexane–benzene (5 : 1—1 : 1) afforded authentic anthracene (210 mg., 20%). Elution with benzene–methylene chloride (1 : 1) then yielded a substance (200 mg.) which appears from its infrared spectrum to be an alcohol, m. p. 154—155° (from *cyclo*hexane).[8a] This by-product is regarded as α-9 : 10-dihydro-9-anthrylbenzyl alcohol (lit.,[8b] m. p. 156—157°) (Found: C, 87·6; H, 6·3. Calc. for $C_{21}H_{18}O$: C, 88·1; H, 6·3%).

Finally a yellow oil (120 mg.) was eluted with chloroform. After removal of solvent, this was treated with *p*-nitrobenzoyl chloride. Chromatography of the hexane solution (10 ml.) of the product on acid-washed alumina (4 g.; Merck) and elution with hexane–benzene (5 : 1) afforded benzyl *p*-nitrobenzoate (30 mg.), identical (mixed m. p. and infrared spectrum) with an authentic specimen.

9-Benzoylanthracene (200 mg.) was refluxed for 4·5 hr. with (i) lithium amide (260 mg.) in dry tetrahydrofuran (10 ml.), (ii) saturated ethanolic potassium hydroxide (20 ml.). In both cases the ketone was recovered practically quantitatively.

2-9′-*Anthryl*-1-1″-*naphthylethane*.—The Grignard reagent was prepared under nitrogen from 2-1′-naphthylethyl bromide (9 g.) and magnesium (0·96 g.) in dry ether (45 ml.). Anthrone (2·5 g.) in dry benzene (45 ml.) was added. The usual working-up gave a solid residue (9·4 g.). Washing with light petroleum afforded greenish-blue fluorescent crystals (2·5 g., 52%), m. p. 169—170° (from hexane–benzene). The *ethane derivative*, m. p. 170—171°, was obtained by low-pressure sublimation; its m. p. was raised to 177—178° by repeated recrystallisation from benzene–hexane (Found: C, 94·0; H, 6·1. $C_{24}H_{20}$ requires C, 93·9; H, 6·1%).

3-9′-*Anthryl*-1-1″-*naphthylpropane*.—3-1′-Naphthylpropyl bromide, $n_D^{16}$ 1·6269, was prepared in 84% yield by refluxing the corresponding primary alcohol with 48% hydrogen bromide. The alcohol (b. p. 130°/0·05 mm.) was prepared in 70% yield by lithium aluminium hydride reduction (in dry ether) of β-1-naphthylacrylic acid, m. p. 210°, prepared (50% yield) by condensation of 1-naphthaldehyde and malonic acid. The Grignard reagent was prepared under nitrogen from the above bromide (5·6 g.) and magnesium (0·54 g.) in dry ether (20 ml.). Anthrone (1·5 g.) in dry benzene (28 ml.) was added. Working-up gave a residual yellow oil which soon solidified. Chromatography on acid-washed alumina (Merck) afforded the desired *propane derivative*, m. p. 92° (from light petroleum–benzene) (20% yield) (Found: C, 93·2; H, 6·6. $C_{27}H_{22}$ requires C, 93·6; H, 6·4%). It was accompanied by 1 : 6-di-1′-naphthylhexane, m. p. 86° (from methyl*cyclo*hexane) (Found: C, 92·2; H, 7·65%; *M*, 360. Calc. for $C_{26}H_{26}$: C, 92·3; H, 7·7%; *M*, 338). Boelhouwer *et al.*[9] report m. p. 86·2—86·6°.

We are indebted to Dr. O. Schnepp for suggesting this problem and to Professor D. Ginsburg for encouragement and advice.

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Haifa, Israel. [*Received, November 11th*, 1957.]

[8] (*a*) Julian, Cole, Diemer, and Schafer, *J. Amer. Chem. Soc.*, 1949, **71**, 2058, report m. p. 114° for α-9-anthrylbenzyl alcohol; (*b*) Horeau and Jacques, *Bull. Soc. chim. France*, 1946, 71.

[9] Boelhouwer, Nederbragt, and Verberg, *Appl. Sci. Res.*, 1950, *A*, **2**, 249, report m. p. 86·2—86·6°.

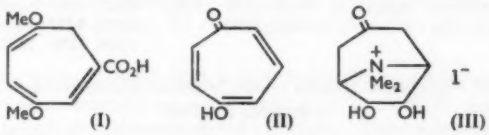
## 358. *Synthetic Experiments in the* cyclo*Heptatrienone Series. Part VII.**

By R. S. Coffey and A. W. Johnson.

4-Hydroxytropone has been synthesised and its physical and chemical properties compared with those of tropolone and 3-hydroxytropone.

Earlier papers in this series described a general method for the synthesis of substituted tropones which depends on the ring expansion of alkoxybenzenes with diazoacetic ester. The products, on hydrolysis, yield alkoxy*cyclo*heptatrienecarboxylic acids which can be decarboxylated and oxidised with bromine to give tropones, and syntheses of tropone-4-carboxylic acid,[1] stipitatic acid,[2,3] puberulic acid,[3] and 3-hydroxytropone [4] by this method have been described. Preliminary experiments directed towards a synthesis of 4-hydroxytropone have also been reported,[5] including the reaction of quinol dimethyl ether with diazoacetic ester which gave a bright yellow acid to which the structure 3 : 6-dimethoxy-*cyclo*heptatrienecarboxylic acid (I; arbitrary placing of double bonds) was assigned. Oxidation of this acid with bromine gave a 4-hydroxytroponecarboxylic acid which however could not be decarboxylated.

Recourse was therefore had to the method already applied in the synthesis of 3-hydroxytropone, which involved decarboxylation of the dimethoxy*cyclo*heptatrienecarboxylic acid before oxidation with bromine. 1 : 4-Dimethoxy*cyclo*heptatriene was thus obtained as a pale yellow oil which was treated with a cooled solution of bromine, to give 4-methoxytropone. Demethylation by hydrogen bromide in acetic acid at 100° then gave 4-hydroxytropone [6] (II) together with a monobromo-substitution product, m. p. 215°, which was easily separated by virtue of its solubility in dilute acid. The yield of 4-hydroxytropone by this method is low and the lack of material has prevented a full investigation of its properties.




Nozoe and his colleagues [7] described the synthesis of 4-hydroxytropone from 4-bromotropone, a by-product from the preparation of 2 : 4 : 7-tribromotropone from *cyclo*heptanone.[7,8] The physical properties of 4-hydroxytropone prepared by the present method agree closely with those quoted by the Japanese authors. More recently, Meinwald and Chapman [9] have described a third synthesis of 4-hydroxytropone, which involves the action of a weak base on teloidinone methiodide (III), although the conditions for the decomposition appear to be critical. The properties of 4-hydroxytropone, like those of tropolone, are modified considerably by the presence of a fused benzene ring as in (IV).[10]

A comparison of the physical properties of the 2-, 3-, and 4-hydroxytropones (Table 1) emphasises the modification of the properties of 2-hyroxytropone (tropolone) caused by hydrogen bonding, *e.g.*, increased volatility, decreased melting point, ferric reaction,

* Part VI, *J.*, 1955, 1841.

[1] Bartels-Keith, Johnson, and Langemann, *J.*, 1952, 4461.
[2] Bartels-Keith, Johnson, and Taylor, *J.*, 1951, 337.
[3] Johns, Johnson, and Murray, *J.*, 1954, 198.
[4] Johns, Johnson, and Tisler, *ibid.*, p. 4604.
[5] Johns, Johnson, Langemann, and Murray, *J.*, 1955, 309.
[6] Coffey, Johns, and Johnson, *Chem. and Ind.*, 1955, 658.
[7] Nozoe, Mukai, Ikegami, and Toda, *ibid.*, p. 66.
[8] Seto, *Sci. Rep. Tôhoku Univ.*, 1953, **37**, 377.
[9] Meinwald and Chapman, *J. Amer. Chem. Soc.*, 1956, **78**, 4816.
[10] Buchanan, *J.*, 1954, 1060.

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decreased acid strength, solubility in non-polar solvents, and the lower position (1615 cm.$^{-1}$) of the carbonyl band in the infrared spectrum. The physical properties of 4-hydroxytropone are rather closer to those of tropolone than are those of 3-hydroxytropone, *e.g.*, the marked bathochromic shift observed in the ultraviolet spectra of 2- and 4-hydroxytropone on formation of the anions, which is not shown by 3-hydroxytropone.

4-Hydroxytropone possesses the expected basic properties, forming a hydrochloride, m. p. 183° (decomp.), and on methylation with diazomethane it is converted into 4-methoxytropone, an oil (or low-melting solid [7]) which was characterised as its picrate. 4-Methoxytropone, which is a vinylogous ester, is hydrolysed to the 4-hydroxy-compound by either acid or alkali. Nozoe *et al.*[7] prepared the benzoate of 4-hydroxytropone and also referred to the formation of a crystalline product with 2 : 4-dinitrophenylhydrazine but

TABLE 1. *The physical properties of* 2-, 3-, *and* 4-*hydroxytropone.*

| | 2-Hydroxytropone [11] (tropolone) | 3-Hydroxytropone [4] | 4-Hydroxytropone |
|---|---|---|---|
| M. p. | 49° | 179—180° | 212° |
| $pK_a$ | 6·7 | 5·4 | 5·65 |
| Volatility | Sublimes at 100°/150 mm. | Sublimes slowly at 130°/0·1 mm. | Sublimes slowly at 130°/0·1 mm. |
| Ferric reaction | Green | — | — |
| Solubility in non-polar solvents | Sol. | Insol. | Insol. |
| Max. (mμ) in ultraviolet spectrum of 95% EtOH soln. | 351, 320, 303 (infl.), 237, 228 | 309, 298, 255, 247 | 333, 226—227 |
| Max. (mμ) in ultraviolet spectrum of 0·1N-NaOH soln. | 393, 330, 234 | 304, 295, 267, 257 | 360, 227—228 |
| Principal max. in infrared spectrum (1650—1150 cm.$^{-1}$) | 1615, 1553, 1475, 1440, 1255 | 1647, 1587, 1550, 1515, 1477, 1443, 1258, 1230, 1196 | 1645, 1600, 1529, 1439, 1282, 1212 |

TABLE 2. *Ultraviolet absorption spectra of the bromine substitution products of tropone and* 4-*hydroxytropone.*

| Compound | Ref. | Ultraviolet max. (mμ) of solutions in 95% EtOH (except where otherwise stated) |
|---|---|---|
| Tropone | 14 | 225, 297, 310 (*iso*octane) |
| 2-Bromotropone | 15 | 246, 315 (*cyclo*hexane) |
| 2 : 7-Dibromotropone | 15 | 262, 335—349 (*cyclo*hexane) |
| 2 : 4 : 7-Tribromotropone | 16 | 272, 340—352 |
| 4-Hydroxytropone | This paper | 227—228, 333 |
| 4-Bromo-5-hydroxytropone | ,, | 223, 351 |
| 2 : 4-Dibromo-5-hydroxytropone | ,, | 246—250, 370 |
| 2 : 4 : 7-Tribromo-5-hydroxytropone | ,, | 262, 396 |

we have been unable to confirm the preparation of the latter derivative and in fact Nozoe [12] has since stated that 4-hydroxytropone is indifferent to ketonic reagents.

Bromination of 4-hydroxytropone with excess of bromine under forcing conditions caused the formation of 2 : 4 : 7-tribromo-5-hydroxytropone (V; R = R′ = R″ = Br), the structure of which has been proved beyond doubt.[13] A monobromo-4-hydroxytropone was obtained as a by-product from the preparation of 4-hydroxytropone (see above) and what appears to be the same compound (ultraviolet spectrum) was obtained in very small yield from a bromination (1 mol. of bromine) of 4-hydroxytropone. The main product from all brominations at room temperature of 4-hydroxytropone has been a dibromo-derivative, m. p. 190°, which was also obtained by further bromination of the monobromo-compound. The action of excess of bromine in hot acetic acid on dibromo-4-hydroxytropone gave 2 : 4 : 7-tribromo-5-hydroxytropone. Thus if it is assumed that the bromine

[11] Doering and Knox, *J. Amer. Chem. Soc.*, 1951, **73**, 828; Koch, *J.*, 1951, 513.
[12] Nozoe, *Fortschr. Chemie org. Naturstoffe*, 1956, **13**, 232.
[13] Nozoe, Kitahara, and Abe, *Proc. Japan Acad.*, 1953, **29**, 347.
[14] Doering and Detert, *J. Amer. Chem. Soc.*, 1951, **73**, 876.
[15] Seto, *Sci. Rep. Tôhoku Univ.*, 1953, **37**, 275.
[16] Nozoe, Kitahara, Ando, and Masamune, *Proc. Japan Acad.*, 1951, **27**, 415.

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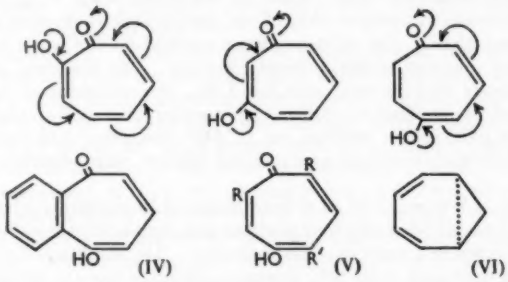
atoms do not rearrange, the monobromo-compound must be the 2-, 5-, or 7-bromo-derivative and, from its ultraviolet spectrum (Table 2), 2- and 7-substitution, which causes a marked bathochromic shift of the lower wave-length band in the spectrum, can be eliminated.

Thus the monobromo-substitution product is 4-bromo-5-hydroxytropone (V; R = R″ = H, R′ = Br) and the dibromo-compound contains bromine in either the 2 : 5- (V; R = R′ = Br, R″ = H) or the 5 : 7-positions (V; R = H, R′ = R″ = Br) of 4-hydroxytropone, of which the latter is favoured for steric and electronic reasons. It is of interest




that the most easily obtainable bromine substitution product of tropolone is the 3 : 5 : 7-tribromo-derivative, with 3-hydroxytropone [4] it is the 2-monobromo-derivative, and with 4-hydroxytropone the 5 : 7-dibromo-compound. In each case these positions are those of high electron density caused by the combined directive effects of the two oxygen atoms.

Qualitative coupling tests showed that 4-hydroxytropone, 4-bromo-5-hydroxytropone, and 5-hydroxytropone-3-carboxylic acid all gave red dyes with diazotised sulphanilic acid, whereas 2 : 4-dibromo-5-hydroxytropone did not. Thus whereas 4-hydroxytropone couples primarily at position 5,[12] it can also couple at position 7 but not 2. This accords with the bromination experiments where substitution occurs preferentially at positions 5 and 7, and only at 2 under forcing conditions.

Re-examination of the product from quinol dimethyl ether and diazoacetic ester has revealed that there are at least three isomeric 3 : 6-dimethoxy*cyclo*heptatrienecarboxylic acids present. The first, m. p. 158—160°, is identical with the product described earlier [5] (where the m. p. was given as 153—154°). The second, isolated in rather greater quantity, has m. p. 138—140°, and the third, m. p. 134—136°, has been obtained only in small quantity. Mixing any two of the acids caused a depression of the melting point. The last was the least stable and the most soluble in organic solvents, and the first was the least soluble. These acids are double-bond isomers of 3 : 6-dimethoxy*cyclo*heptatrienecarboxylic acid (*e.g.*, I) as all three have the same ultraviolet absorption; after oxidation with bromine and hydrolysis with hydrogen bromide, all gave 5-hydroxytropone-3-carboxylic acid. It is of interest that Doering *et al.*[17] recently assigned structures to all four of the double-bond isomers of *cyclo*heptatrienecarboxylic acid (the Buchner acids) by use of nuclear magnetic resonance and identification of the products of thermal decomposition of the Diels–Alder adducts with diethyl acetylenedicarboxylate, and they present evidence to suggest that the acids are derivatives of tropilidene (VI) which has a planar $\psi$-aromatic structure in contrast to *cyclo*heptatriene.

## Experimental

Ultraviolet spectra were determined for 95% EtOH solutions, and infrared spectra for Nujol mulls except where otherwise stated.

3 : 6-*Dimethoxy*cyclo*heptatrienecarboxylic Acid* (cf. Johns, Johnson, Langemann, and

[17] Doering, Laber, Vonderwahl, Chamberlain, and Williams, *Proc. Japan Acad.*, 1956, **78**, 5448.

Murray [6]).—The crude acid (5 g.), prepared in the manner already described, was fractionally crystallised from benzene–light petroleum (b. p. 60—80°), the following isomers being obtained: Acid A (0·45 g.), m. p. 158—160°, identical with the acid obtained previously; [5] the infrared spectrum showed main maxima at 1670, 1618, 1532, 1472, 1423, 1378, 1357, 1287, 1257, 1221, 1205, 1167, and 1133 cm.$^{-1}$. *Acid B* (0·52 g.), m. p. 138—140° (Found: C, 61·3; H, 6·6. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%); the infrared spectrum showed main maxima at 1690, 1657, 1617, 1553, 1465, 1443, 1369, 1336, 1287, 1255, 1201, 1182, and 1152 cm.$^{-1}$. Acid C (30 mg.), m. p. 134—136°; the infrared spectrum showed main maxima at 1689, 1620, 1563, 1471, 1432, 1366, 1333, 1282, 1215, 1180, and 1167 cm.$^{-1}$.

*5-Hydroxytropone-3-carboxylic Acid.*—Each of the above acids A, B, and C was dissolved separately in the minimum quantity of chloroform, and the solutions were treated with bromine (1 mol.) in chloroform at 0°. The mixtures were warmed on the water-bath for 10 min. and the solvent was then removed under reduced pressure. The resulting gums were heated at 100° with 48% aqueous hydrobromic acid for 1 hr., the solvent was again removed under reduced pressure, and the residues crystallised from water (charcoal) to give 5-hydroxytropone-3-carboxylic acid as pale yellow needles, m. p. 240° (decomp.); in each case the physical properties, particularly the ultraviolet and infrared spectra, were identical with those recorded earlier.[5]

*4-Hydroxytropone.*—A mixture of 3 : 6-dimethoxy*cyclo*heptatrienecarboxylic acid (2 g.) and copper bronze (40 g.) was divided into four portions and each heated rapidly in a soda-glass tube, and the distillate collected in a receiver cooled below 0°. The combined distillates were dissolved in ether (60 c.c.) and extracted with 10% aqueous sodium carbonate solution (3 × 20 c.c.), the ethereal solution dried, and the solvent removed. The residual dark viscous oil (0·14 g.) was distilled, to give crude 1 : 4-dimethoxy*cyclo*heptatriene as a pale yellow oil (0·1 g.), b. p. 95—110°/0·2 mm.

This product was dissolved in chloroform (5 c.c.), cooled to 0°, and then treated with a solution of bromine (1 mol.) in chloroform. After 10 min., the solvent was removed at atmospheric pressure on the water-bath, hydrogen bromide being evolved. The residue was hydrolysed by heating it for 1 hr. with 20% hydrobromic acid (6 c.c.), after which the solvent was removed under reduced pressure. The residue was dissolved in hot water, and the solution kept overnight; a yellow solid (51 mg.), m. p. 198°, was obtained. This was crude 4-bromo-5-hydroxytropone and its further purification is described below. The filtrate obtained after separation of the bromo-compound was evaporated to dryness and the residual brown gum digested with acetone. The colourless solid (36 mg.) which separated was the hydrobromide of 4-hydroxytropone. It was soluble in water and the solution gave an immediate precipitate with silver bromide. It was sublimed at 120°/2 × $10^{-4}$ mm., giving pale yellow 4-hydroxytropone (21 mg.), m. p. 212° (Nozoe *et al.*[7] give m. p. 212°) (Found: C, 68·7; H, 5·0. Calc. for $C_7H_6O_2$: C, 68·85; H, 4·95%). Light absorption: (i) max. at 333 and 226—227 mμ (log ε 4·14 and 4·28), min. at 268 mμ (log ε 2·72); (ii) in 0·1N-NaOH, max. at 360 and 227 mμ (log ε 4·34 and 4·30), min. at 284 mμ (log ε 2·77). The infrared spectrum showed main max. at 2440 (broad), 1645, 1621, 1600, 1529, 1439, 1399, 1282, and 1212 cm.$^{-1}$.

4-Hydroxytropone was soluble in water, alcohols, acetone, dioxan, and acetic acid. It was almost insoluble in benzene, chloroform, and light petroleum. Its aqueous solution was acidic to litmus and its p$K$ in water at 20° was 5·65. Alkaline solutions were pale greenish-yellow. It gave no ferric reaction and did not react with 2 : 4-dinitrophenylhydrazine. The hydrochloride, m. p. 183°, was formed by bubbling dry hydrogen chloride through a solution in glacial acetic acid. It decomposed at 140°/0·2 mm., 4-hydroxytropone being re-formed and obtained as a sublimate. The picrate crystallised from aqueous methanol as yellow needles, m. p. 85—87° (lit.,[7] 90°) (rapid heating; the picrate decomposed below its m. p. to 4-hydroxytropone and picric acid) (Found: C, 43·95; H, 2·95; N, 12·05. Calc. for $C_{13}H_9O_9N_3$: C, 44·45; H, 2·6; N, 12·0%). 4-Hydroxytropone was regenerated from its picrate when the ethanolic solution was shaken with a slight excess of Dowex 2 resin in the hydroxide form.

*4-Methoxytropone.*—A methanolic solution (5 c.c.) of 4-hydroxytropone (35 mg.) was treated with excess of ethereal diazomethane. After 30 min. the solvent was removed under reduced pressure and the residual brown gum sublimed at 60—70°/0·5 mm., to give a colourless oil which rapidly resinified in air. Light absorption max. at 324—325 and 222 mμ (log ε 3·80 and 4·11), min. at 265 mμ (log ε 2·75). The picrate formed yellow needles, m. p. 131° (lit.,[7] 132—133°) (Found: C, 46·7; H, 3·05; N, 11·4. Calc. for $C_{14}H_{11}O_9N_3$: C, 46·0; H, 3·0; N, 11·4%).

The picrate was reconverted into the free base by Dowex 2 resin as in the case of 4-hydroxytropone, and 4-methoxytropone was converted into 4-hydroxytropone by 20% hydrobromic acid at room temperature.

*4-Bromo-5-hydroxytropone.*—(i) *From* 3 : 6-*dimethoxy*cyclo*heptatrienecarboxylic acid.* The crude product, m. p. 198°, described above as a by-product in the preparation of 4-hydroxytropone, was sublimed at 140°/0·2 mm. and then crystallised from aqueous ethanol, to give pale yellow needles, m. p. 215° (Found: C, 41·9; H, 2·6. $C_7H_5O_2Br$ requires C, 41·8; H, 2·5%). Light absorption max. at 351 and 222—223 mμ (log ε 4·09 and 4·23), min. at 276—277 mμ (log ε 3·05), and an inflection at 234—236 mμ (log ε 4·18). The infrared spectrum showed max. at 1639, 1587, 1541, 1449, 1383, 1313, 1277, 1259, 1214, 1117, 931, 857, 822, 788, 768, 740, and 712 cm.$^{-1}$. The p$K$ in water at 20° was 4·9.

(ii) *From 4-hydroxytropone.* A slightly impure preparation of the monobromo-compound was isolated as a by-product from the bromination of 4-hydroxytropone with 1 mol. of bromine (see below). Removal of the solvent from the alcoholic extract gave a gum (20 mg.) from which a pale yellow solid (8 mg.), m. p. 164—166°, was obtained after sublimation. The m. p. was raised to 194—196° (not depressed when mixed with an authentic specimen of 4-bromo-5-hydroxytropone), on re-sublimation at 130°/0·05 mm. (Found: C, 41·3; H, 2·7%).

2 : 4-*Dibromo-5-hydroxytropone.*—(i) *From 4-hydroxytropone.* A stirred solution of 4-hydroxytropone (100 mg.) in glacial acetic acid (12 c.c.) at 10° was treated slowly with a solution of bromine (1 mol.) in acetic acid. Then the solution was kept for 20 min. and next heated on the steam-bath for 10 min. After a further 3 hr. at room temperature a yellow solid had separated which was removed by filtration and crystallised from aqueous methanol, to give 2 : 4-*dibromo-5-hydroxytropone* as pale yellow needles (96 mg.), m. p. 192° (Found: C, 30·2; H, 1·8. $C_7H_4O_2Br_2$ requires C, 30·0; H, 1·4%), $\lambda_{max.}$ 368—369 and 240—246 mμ (log ε 4·12 and 4·23), $\lambda_{min.}$ 284 and 212 mμ (log ε 3·1 and 4·03), $\nu_{max.}$ 1623, 1546, 1471, 1439, 1348, 1295, 1274, 1250, 1153, 990, 920, 845, 802, and 778 cm.$^{-1}$.

The acetic acid solution was evaporated under reduced pressure and the residue extracted with chloroform (4 × 10 c.c.). The insoluble residue (21 mg.) was sublimed at 140°/0·2 mm., to give unchanged 4-hydroxytropone. The chloroform extract was evaporated and the solid so obtained crystallised from aqueous methanol, to give brown needles which were further purified by sublimation at 140°/0·2 mm., a bright yellow solid, m. p. 218°, being obtained. This was a mixture of di- and tri-bromotropones (Found: C, 26·6; H, 1·3%), $\lambda_{max.}$ 387 and 251—259 mμ. The methanolic solution was treated as described in the previous experiment and yielded 4-bromo-5-hydroxytropone.

In another experiment 4-hydroxytropone (70 mg.) in acetic acid at 10° was treated with bromine (3 mol.) also in acetic acid. The mixture was kept for 20 min. at room temperature, then heated at 100° for 10 min. as before, and on cooling 2 : 4-dibromo-5-hydroxytropone (115 mg.) crystallised. A further quantity (11 mg.; total yield 75%) was obtained by concentration of the filtrate. The product was identical with that obtained in the previous experiment.

(ii) *From 4-bromo-5-hydroxytropone.* The monobromo-compound (16 mg.) was dissolved in acetic acid (5 c.c.) and treated with a solution of bromine (1 mol.) in acetic acid at room temperature. After the addition, the solution was concentrated, and diluted with water, yellow 2 : 4-dibromo-5-hydroxytropone (21 mg.) being precipitated. After crystallisation from aqueous methanol, this had m. p. 192°, undepressed on admixture with the sample prepared directly from 4-hydroxytropone. The ultraviolet and infrared spectra also corresponded with those of the previous product.

2 : 4 : 7-*Tribromo-5-hydroxytropone.*—A solution of 4-hydroxytropone (14 mg.) in acetic acid (3 c.c.) at 100° was treated with a solution of bromine (5 mol.) in acetic acid. When the mixture was kept overnight at room temperature, yellow needles (25 mg.), m. p. 231° raised to 236° (lit.,[13] 239°) on crystallisation from ethanol, were obtained (Found: C, 23·75; H, 0·7. Calc. for $C_7H_3O_2Br_3$: C, 23·4; H, 0·8%). Light absorption max. were at 396 and 262 mμ (log ε 4·31 and 4·34), min. at 298 and 232 mμ (log ε 3·18 and 4·06). The same product was obtained from a similar bromination of 2 : 4-dibromo-5-hydroxytropone.

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## 359. *The Ultraviolet Absorption Spectra and Stability Constants of Cuprous Cyanide Complexes.*

By E. A. Simpson and Gwyneth M. Waind.

The optical densities of aqueous solutions of cuprous cyanide and potassium or sodium cyanide have been measured at 25° and used to derive the molar extinction coefficients of the anions $[Cu(CN)_2]^-$, $[Cu(CN)_3]^{2-}$, and $[Cu(CN)_4]^{3-}$ from 220 to 320 mμ. The association constant $K_3 = [Cu(CN)_3^{2-}]/[Cu(CN)_2^-][CN^-]$ is $1{\cdot}27 \times 10^4$ at an ionic strength of about 0·001. The equilibria are all adequately described by the constants derived by earlier workers from infrared spectra.

The ultraviolet absorption spectra of the complex cuprous cyanides are compared with those of other metal cyanides.

While studying plating solutions we had to determine the change in the composition of cuprous cyanide solutions with increasing concentration of added cyanide ion, and found the ultraviolet absorption spectrum a convenient property to measure. Meanwhile, Penneman and Jones,[1] from the infrared absorption spectra of aqueous solutions, determined both concentration and thermodynamic dissociation constants for the equilibria:

$$[Cu(CN)_3]^{2-} \rightleftharpoons [Cu(CN)_2]^- + CN^-; \quad [Cu(CN)_4]^{3-} \rightleftharpoons [Cu(CN)_3]^{2-} + CN^-$$

and Brigando[2] reported the ultraviolet absorption spectra of a number of metal cyanides. However, the solution used by Brigando to measure the spectrum of $[Cu(CN)_4]^{3-}$ contained all three species. The results now reported for very dilute solutions agree well with those from the infrared measurements at much higher concentrations.

### Experimental

All measurements were made with a Unicam S.P. 500 spectrophotometer in water-jacketed silica cells at 25° ± 0·02°.

Cuprous cyanide, from " AnalaR " cupric sulphate and potassium cyanide, was dissolved in excess of potassium cyanide solution and reprecipitated with a slight excess of sulphuric acid. The pure white solid was washed with conductivity water and alcohol and dried at 110°. All solutions were prepared from this and recrystallised potassium or sodium cyanide. They were standardised for total cyanide, after distillation, by titration with silver nitrate, and for copper either volumetrically or, for the most dilute solutions, colorimetrically as the *o*-phenanthroline complex. Conductivity water saturated with nitrogen was used throughout. The solutions with total cyanide : copper ratios of less than 2·6 were prepared by adding small known volumes of standard acid (hydrochloric or perchloric) to the cuprocyanide solutions in stoppered flasks.

*Results.*—The absorption spectra all have two large peaks (with maximum apparent molar extinction coefficients, $\varepsilon_{app.}$, greater than 1000) at about 210 and 235 mμ. For solutions containing less than 1·0mM-copper and increasing cyanide concentration there are two isosbestic points. For these solutions $\varepsilon_{app.}$ at 238 mμ increases linearly with increasing ratio of total cyanide to total copper up to about 4·5 (Fig. 1). For more concentrated solutions at this wavelength there is a sharp increase up to ratios of about 3 and then a maximum at about 4. Duplicate solutions with sodium cyanide instead of potassium cyanide gave identical absorption spectra.

*Treatment of Results.*—Cyanide ion is hydrolysed[3] mainly to cyanate and hydrogen cyanide; hydrogen cyanide gives ammonium formate.[4] We therefore measured the absorbance of solutions of potassium cyanide, sodium cyanate, and sodium formate (Table 1). In all cases the molar extinction coefficients are too small for the concentrations expected to introduce any

[1] Penneman and Jones, *J. Chem. Phys.*, 1956, **24**, 293.
[2] Brigando, *Bull. Soc. chim. France*, 1957, **4**, 503.
[3] For a review see Deltombe and Pourbaix, Proc. of 6th C.I.T.C.E., London, 1956, p. 138.
[4] Marsh and Martin, *J. Appl. Chem.*, 1957, **7**, 205.

errors into the treatment given below; however, because of this hydrolysis the pH could only be used to calculate the hydrogen cyanide concentration in the most alkaline solutions (pH >10).

TABLE 1.

| Wavelength | Molar extinction coefficient | | |
|---|---|---|---|
| (mμ) | $CN^-$ | $CNO^-$ | $HCO_3^-$ |
| 250—320 | | <0·1 | |
| 240 | — | 0·2 | 0·1 |
| 238 | 8·0 | — | — |
| 235 | — | 0·2 | 0·4 |
| 230 | 13·5 | 0·3 | 1·2 |
| 225 | 18·2 | 0·4 | 3·5 |
| 220 | 20·0 | 0·8 | 8·1 |

TABLE 2.

| Total Cu | Total CN | pH | *a* | *b* | *c* | $[CN^-]_{free}$ |
|---|---|---|---|---|---|---|
| 1·512 | 13·000 | 10·57 | 0·004 | 0·838 | 0·675 | 7·338 |
| 1·512 | 10·100 | 10·49 | 0·007 | 0·991 | 0·519 | 4·673 |
| 1·512 | 7·785 | 10·28 | 0·014 | 1·199 | 0·305 | 2·733 |
| 1·264 | 8·015 | 10·53 | 0·009 | 0·943 | 0·312 | 3·536 |
| 1·264 | 6·627 | 10·48 | 0·013 | 1·040 | 0·211 | 2·307 |

The thermodynamic dissociation constants calculated by Penneman and Jones [1] are given in equations (1)—(6), which were used to determine the compositions of solutions containing more than 1·0mM-copper and high cyanide ratios. The only assumptions are that eqn. (1)

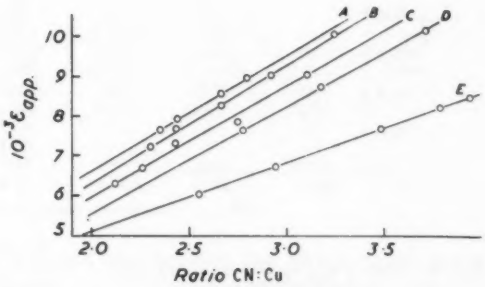



FIG. 1. *Relation of* $\varepsilon_{app.}$ *to* CN : Cu *ratio at* 238 mμ.

Copper: *A*, 0·6883; *B*, 0·4818; *C*, 0·3658; *D*, 0·3093; *E*, 0·2434 mM.

holds for these very alkaline solutions; that corrections for the ionic activity coefficients (which change very little) can be expressed in terms of eqn. (2); and that all the copper is in the form of a complex. In these equations square brackets represent molar concentrations, the enclosing brackets denoting complex ions being omitted.

$$\log_{10}[HCN] = \overline{14} + pH + 0{\cdot}5f(I) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$f(I) = I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}); \text{ where } I = \text{ionic strength} \quad . \quad . \quad . \quad . \quad (2)$$

$$[Cu(CN)_3^{2-}] = b = \text{Total copper}/(1 + X + Y) \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\log_{10} X = \overline{5}{\cdot}4150 + f(I) - \log_{10}[CN^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$\log_{10} Y = 1{\cdot}7160 + 3f(I) + \log_{10}[CN^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

$$[Cu(CN)_4^{3-}] = c = bY$$

$$[Cu(CN)_2^-] = a = \text{Total copper} - b - c$$

$$[CN^-] = [K^+] - [HCN] - a - 2b - 3c \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$X$ and $Y$ are $a/b$ and $c/b$ respectively.

The calculated compositions (mmoles/l.) are given in Table 2. These, combined with the measured optical densities ($x$) at 238 mμ (Fig. 2), show that $x/b$ is linear with $c/b$. The values of $\varepsilon$ for $Cu(CN)_3^{2-} = \varepsilon_3$ and for $Cu(CN)_4^{3-} = \varepsilon_4$ at λ 238 mμ from the intercept and slope are 11,600 and 10,050 respectively.

*Treatment of Dilute Solutions given in Fig.* 1.—These solutions were assumed to contain only

$[Cu(CN)_3]^-$, and $[Cu(CN)_3]^{2-}$, both absorbing at 238 mμ. The concentration of hydrogen cyanide was ignored and the following equations used {$\varepsilon_1$ applies to $[Cu(CN)_2]^-$}:

$$a + b = \text{Total copper} = y$$

$$\varepsilon_{app.} = (a/y)\varepsilon_1 + (b/y)\varepsilon_2$$

$$= \varepsilon_1 + \alpha_2(\varepsilon_2 - \varepsilon_1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$2a + 3b + [CN^-]_{free} = \text{total cyanide};\ b/a = K_3[CN^-]_{free}$$

$$(\text{Total cyanide/Total copper}) - 2 = Z.$$

FIG. 2. *Plots of c/b against x/b at (A) 235 mμ and (B) 238 mμ.*

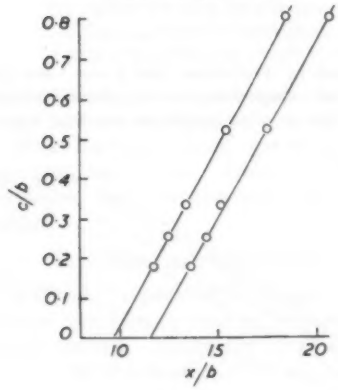



FIG. 3.

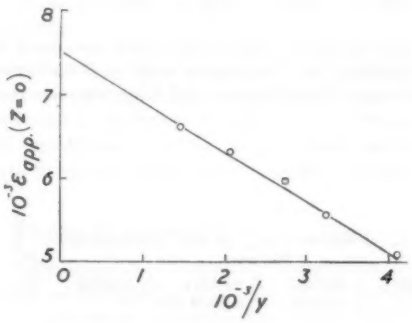



FIG. 4. *Plots of $\varepsilon_{app.}$ against $\alpha_2$ at (A) 205 mμ and (B) 238 mμ.*

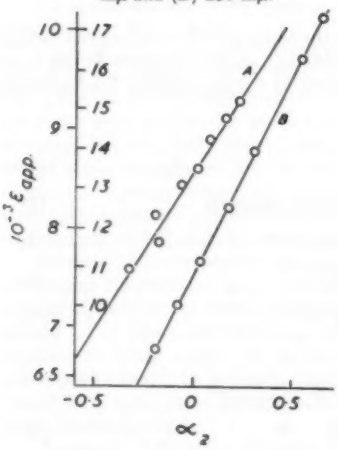
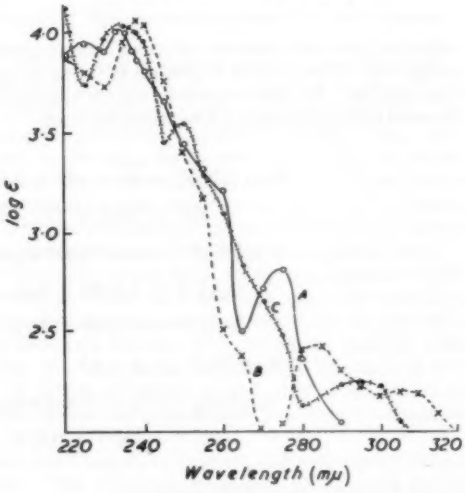



FIG. 5. *Ultraviolet spectra of (A) $[Cu(CN)_2]^-$, (B) $[Cu(CN)_3]^{2-}$, and (C) $[Cu(CN)_4]^{3-}$.*




Therefore, by substitution in eqn. (7)

$$\varepsilon_{app.} = Z\varepsilon_2/\{1 - (1/Ky)[1 \div (1 - \alpha_2)]\} + (1 - \alpha_2)\varepsilon_1 \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Equation (8) was used by reading the values of the apparent extinction coefficients extrapolated to $Z = 0$ from Fig. 1 and plotting them against $1/y$ (Fig. 3). The intercept $\varepsilon_1$ is

7540 and $1/K_3$, found by dividing the slope by $\varepsilon_1$, is $7{\cdot}85 \times 10^{-5}$, giving $K_3 = 1{\cdot}27 \times 10^4$: the ionic strength of these solutions varied from 0·0006 to 0·0012. When this value was substituted in eqn. (4), $x/b$ was altered by less than 1% and $c/b$ by less than 0·3% which did not alter the calculated extinction coefficients $\varepsilon_2$ and $\varepsilon_3$ by as much as the experimental error of ±1%. Optical densities at below 230 mμ needed correction for the absorption of $[Cu(CN)_2]^-$, although this was always less than 2%. The values of $\varepsilon_2$ and $\varepsilon_3$ plotted in Fig. 5 were obtained in this way.

$\varepsilon_1$ at other wavelengths was obtained from the apparent extinction coefficients plotted in Fig. 3 by using the values of $\varepsilon_1$ and $\varepsilon_2$ at 238 mμ to calculate $\alpha_2$ [eqn. (7)]. Typical plots of $\alpha_2$ against $\varepsilon_{app.}$ are given in Fig. 4. $\varepsilon_1$ and $\varepsilon_2$ at different wavelengths were read from such graphs. The values of $\varepsilon_2$ from both sets of solutions agreed within experimental error.

## Discussion

The positions and maximum extinction coefficients for the three copper complexes are given in Table 3. The data for $[Au(CN)_2]^-$ and $[Ni(CN)_4]^{2-}$ were given by Brigando.[2]

Table 3.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $[Cu(CN)_2]^-$ | $\lambda_{max.}$ (mμ) | 225 | 234 | (260) | 274 | — | — |
| | $\log_{10} \varepsilon_{max.}$ | 3·962 | 4·025 | (3·214) | 2·813 | — | — |
| $[Cu(CN)_3]^{2-}$ | $\lambda_{max.}$ | — | 238 | (255) | (265) | 285 | 305 |
| | $\log_{10} \varepsilon_{max.}$ | — | 4065 | (3·176) | (2·731) | 2·415 | 2·204 |
| $[Cu(CN)_4]^{3-}$ | $\lambda_{max.}$ | — | 235 | 250 | (275) | 295 | — |
| | $\log_{10} \varepsilon_{max.}$ | — | 4·041 | 3·549 | (2·477) | 2·230 | — |
| $[Au(CN)_2]^-$ | $\lambda_{max.}$ | 230 | 240 | — | — | — | — |
| | $\log_{10} \varepsilon_{max.}$ | 3·02 | 3·50 | — | — | — | — |
| $[Ni(CN)_4]^{2-}$ | $\lambda_{max.}$ | — | 268 | 288 | 310 | 328 | — |
| | $\log_{10} \varepsilon_{max.}$ | — | 4·02 | 3·60 | 2·83 | 2·64 | — |

Parentheses indicate shoulders.

The similarities between the two linear ions and also between the higher complexes is obvious. This pattern has also been found for the hexacyanides of some tervalent transition-metal ions.[2] It has been shown [5] that not only for those transition-metal complexes which are usually assumed to be chiefly "ionic" but also for the mono- and tris-dipyridyl and *o*-phenanthroline complexes, similar intense ultraviolet bands may be considered to be derived from those of the ligands which are shifted towards longer wavelengths by *electrostatic* interaction with the metal ion. For the hexacyanides the red shift increases in the order Fe < Co < Cr < Mn, which suggests that this simple picture is also applicable to these complexes. The general pattern of the spectra for copper and gold remains the same as that of transition-metal complexes; silver cyanide solutions absorb below 220 mμ. There is no correlation here between charge and radius of the metal ion and the red shift, which does however increase with increasing stability as measured by the dissociation constants which are given here for the three copper complexes and which for the singly charged cyanides indicate decreasing stability in the order gold > copper > silver.[1]

The authors thank S.E.R.L. (Harlow) for a maintenance grant (to E. A. S.).

Queen Mary College, London, E.1. [*Received, December 9th*, 1957.]

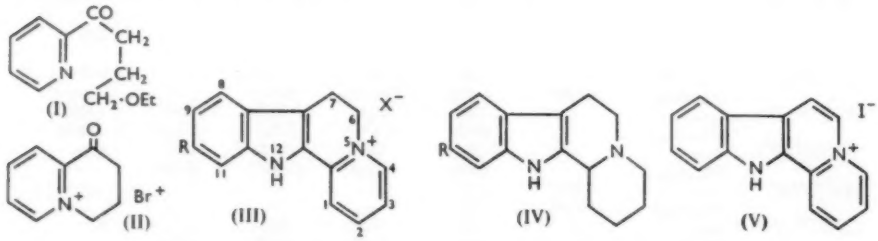
[5] Schläfer, *Z. phys. Chem.* (*Frankfurt*), 1956, **8**, 373.

## 360. *Quinolizines. Part I. Synthesis of Some Indolo*[2,3-a]*quinolizine and Benz*[g]*indolo*[2,3-a]*quinolizine Derivatives.*

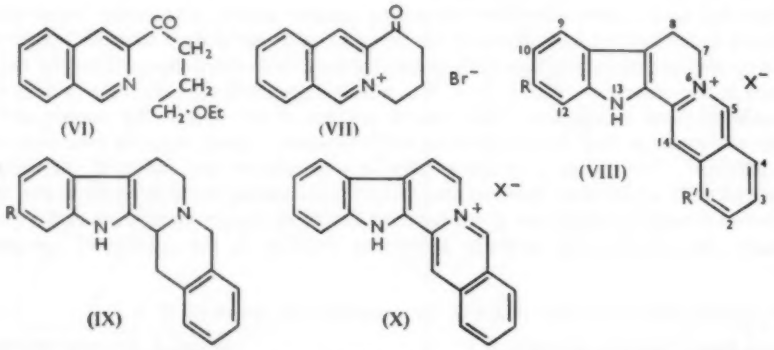
By E. E. Glover and Gurnos Jones.

A general synthesis of 6 : 7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium salts (III) and of 7 : 8-dihydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium salts (VIII) is described. The compound (III; R = H, X = I) has been dehydrogenated to 12*H*-indolo(2,3-*a*)quinolizinium iodide (V).

We describe below a general method by which 6 : 7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium (III) and 7 : 8-dihydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium salts (VIII) can be prepared. Dehydrogenation of the dihydro-compound (III) gives an indolo[2,3-*a*]-quinolizinium salt (V); hydrogenation of pentacyclic compounds of type (VIII) gives derivatives of hexadehydroyohimban (IX).




A previous synthesis [1] of the dihydro-compound (III; R = H, X = Br) uses a seven-stage route from 2-2′-pyridylindole. We started from 1 : 2 : 3 : 4-tetrahydro-1-oxoquinolizinium bromide (II), prepared, as briefly reported,[2] from 2-γ-ethoxybutyrylpyridine [3] (I). The ketone (I) was treated with boiling hydrobromic acid, and the intermediate bromo-ketone was cyclized in boiling chloroform, giving the bicyclic ketone (II)



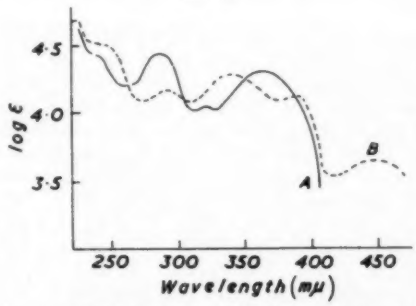

(79%), whose phenylhydrazone was isolated as a water-insoluble iodide; this was cyclized in high yield by anhydrous ethanolic hydrogen chloride to the dihydroindoloquinolizinium salt (III; R = H). Catalytic reduction of this gave 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-octahydro-12*H*-indolo[2,3-*a*]quinolizine (IV; R = H). An attempt to dehydrogenate the dihydro-compound (III; R = H, X = I) with mercuric acetate was unsuccessful; a

[1] Sugasawa, Terashima, and Kanaoka, *Pharm. Bull.* (*Japan*), 1956, **4**, 16.
[2] Glover and Jones, *Chem. and Ind.*, 1956, 1456.
[3] Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 1144.

water-insoluble complex was isolated, containing mercury, from which the dihydro-compound was recovered unchanged. The dehydrogenation was accomplished with acid palladium–charcoal,[4] 12*H*-indolo[2,3-*a*]quinolizinium iodide (V) being isolated. The ultraviolet absorption of this iodide (V) in neutral and in alkaline solution closely paralleled that of sempervirine [5] and of other alkylated indoloquinolizinium compounds,[4,6] of which the compound (V) contains the parent cation (Fig. 1).

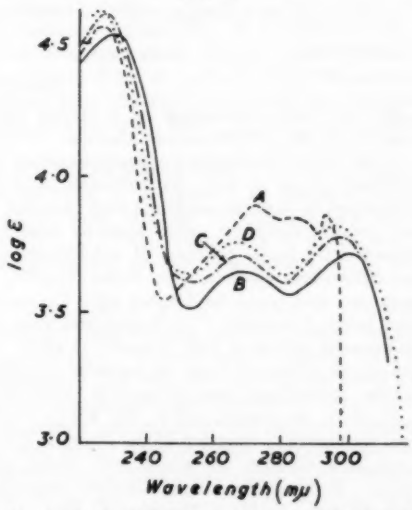
For the synthesis of the pentacyclic compounds the starting material was 3-γ-ethoxybutyryl*iso*quinoline (VI), prepared by the action of 3-ethoxypropylmagnesium bromide on 3-cyano*iso*quinoline. Cyclization gave 1 : 2 : 3 : 4-tetrahydro-1-oxobenzo[*b*]quinolizinium bromide (VII) which was converted into its phenylhydrazone iodide. Indolization then

FIG. 1.




*A*, 12H-*Indolo*[2,3-a]*quinolizinium iodide in ethanol*; *B*, *indolo*[2,3-a]*quinolizinium iodide in* 0·01N-*alcoholic* KOH.

FIG. 2.




*A*, 1 : 2 : 3 : 4-*Tetrahydro-5-methoxycarbazole*; [8] *B*, 1 : 2 : 3 : 4-*tetrahydro-7-methoxycarbazole*; [8] *C*, 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*octahydro*-10-*methoxyindolo*[2,3-a]*quinolizine in* EtOH; *D*, 5 : 7 : 8 : 13 : 13*b* : 14-*hexahydro*-11-*methoxy*-13H-*benz*[g]*indolo*[2,3-a]*quinolizine in* MeOH.

gave 7 : 8-dihydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium iodide (VIII; R = R′ = H, X = I), the properties of which were in good agreement with those recorded by Swan [7] for the compound obtained by the action of iodine in acetone on the hexadehydroyohimban (IX; R = H). Attempts to dehydrogenate the dihydro-compound (VIII; R = R′ = H, X = I) have so far failed to give any of the completely aromatic pentacyclic compound (X).

Since one of the objectives of this work was a synthetic route to alstoniline chloride (VIII; R = OMe, R′ = $CO_2Me$, X = Cl), the *m*-methoxyphenylhydrazones of the ketones (II) and (VII) were prepared and cyclized to the indoles (III; R = OMe, X = I) and (VIII; R = OMe, R′ = H, X = I) respectively. The position of the methoxyl group was proved by catalytic hydrogenation of the dihydro-salts to the hexahydro-compound (IV; R = OMe) and the tetrahydro-compound (IX; R = OMe) respectively. Both these compounds

[4] Cf. Schwyzer, *Helv. Chim. Acta*, 1952, **35**, 867.
[5] Prelog, *ibid.*, 1948, **31**, 588.
[6] Goutarel, Janot, and Perezamador y Barron, *Bull. Soc. chim. France*, 1954, 863.
[7] Swan, *J.*, 1949, 1720.
[8] Chalmers, Openshaw, and Smith, *J.*, 1957, 1115.

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showed ultraviolet absorption almost identical with that of 1 : 2 : 3 : 4-tetrahydro-7-methoxycarbazole [8] and different from that of 1 : 2 : 3 : 4-tetrahydro-5-methoxycarbazole [8] (Fig. 2), indicating the presence of a methoxyl group in the 6-position of the indole nucleus. Thus the direction of cyclization of the *m*-methoxyphenylhydrazones is that predicted by Ockenden and Schofield,[9] who found that the introduction of groups which are *ortho-para*-directing in electrophilic substitution, into the 3-position of a phenylhydrazone, led to the preponderance of the 6-substituted indole after cyclization. The ultraviolet absorption of 7 : 8-dihydro-11-methoxy-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium iodide (VIII; R = OMe, R′ = H, X = I) was very similar to that of alstoniline chloride,[10] and the salts of the tetrahydro-compound (IX; R = OMe) were readily oxidized in air to more highly coloured materials, as is reported for the salts of tetrahydroalstoniline.[11]

After completion of this work synthesis of the compounds (III; R = H) and (VIII; R = R′ = H) by a similar route was reported by Jacobs and Fouché.[12]

## Experimental

M. p.s were determined on a Kofler block. Ultraviolet absorption was determined for solutions in 95% EtOH unless otherwise stated.

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxoquinolizinium Bromide* (II).—A solution of 2-γ-ethoxybutyrylpyridine [3] (3 g.) in 35% hydrobromic acid (25 ml.) was boiled under reflux for 1 hr., then evaporated to dryness under reduced pressure. The solid residue was dissolved in water (25 ml.) and treated dropwise with aqueous sodium carbonate, the liberated bromo-amine being extracted by small portions of chloroform until the aqueous layer became deep orange-red. The chloroform extracts were dried ($Na_2SO_4$) and boiled under reflux until the solid bromide separated and could be filtered off. Concentration of the chloroform filtrate gave a further small yield of bromide. Recrystallized from absolute ethanol as colourless needles (2·8 g., 79%) the bromide had m. p. 198° (Found: C, 47·1; H, 4·2. Calc. for $C_9H_{10}ONBr$: C, 47·4; H, 4·4%). The *picrate*, obtained from an aqueous solution of the bromide by addition of aqueous sodium picrate, crystallized from ethanol as yellow needles, m. p. 161—162° (Found: C, 48·0; H, 3·2. $C_{15}H_{13}O_8N_4$ requires C, 47·9; H, 3·2%). The *phenylhydrazone iodide* was prepared in 91% yield by heating a solution of the bromide (II) with a slight excess of phenylhydrazine in glacial acetic acid, diluting the whole with water, and precipitating the product by aqueous sodium iodide. Recrystallized from absolute ethanol as yellow needles, it had m. p. 239° (Found: C, 49·6; H, 4·4. $C_{15}H_{16}N_2I$ requires C, 49·4; H, 4·4%), $\lambda_{max.}$ 2430, 4100 Å ($\log_{10}\varepsilon$ 4·07, 4·48).

The m-*methoxyphenylhydrazone iodide*, prepared as above, crystallized from absolute ethanol as yellow prisms, m. p. 255° (Found: C, 48·3; H, 4·5. $C_{16}H_{18}ON_2I$ requires C, 48·6; H, 4·6%), $\lambda_{max.}$ 2680, 4120 Å ($\log_{10}\varepsilon$ 3·88, 4·51).

6 : 7-*Dihydro*-12H-*indolo*[2,3-a]*quinolizinium Iodide* (III; R = H, X = I).—The phenylhydrazone iodide (2·3 g.) in anhydrous ethanol was saturated with dry hydrogen chloride at 0°. The solution was then boiled under reflux for 2 hr. Evaporation to dryness gave a solid, which was dissolved in water and treated with aqueous sodium iodide. The precipitated *iodide* crystallized from absolute ethanol as yellow needles, m. p. 298° (decomp.) (1·96 g., 89%) (Found: C, 51·8; H, 3·6. $C_{15}H_{13}N_2I$ requires C, 51·75; H, 3·8%), $\lambda_{max.}$ 2520, 3150, 3890 Å ($\log_{10}\varepsilon$ 3·52, 3·79, 3·74). The *picrate*, orange plates (from absolute ethanol), had m. p. 247° (Found: C, 56·35; H, 3·4. $C_{21}H_{15}O_7N_5$ requires C, 56·1; H, 3·4%).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*Octahydroindolo*[2,3-a]*quinolizine* (IV; R = H).—The iodide (III; R = H, X = I) in dry ethanol, over Adams catalyst, was hydrogenated to completion at atmospheric pressure and temperature. Filtration, and evaporation of the filtrate, gave the solid *hydriodide*, recrystallizing from absolute ethanol as plates, m. p. 237—238° (Found: C, 50·5; H, 5·9. $C_{15}H_{19}N_2I$ requires C, 50·9; H, 5·4%). The picrate crystallized from absolute ethanol as yellow needles, m. p. 230° (lit.,[1] m. p. 230—232°). The free base crystallized from light petroleum (b. p. 60—80°) as colourless needles, m. p. 149—150° (lit.,[1] m. p. 150—150·5°).

[9] Ockenden and Schofield, *J.*, 1957, 3175.
[10] Elderfield and Wythe, *J. Org. Chem.*, 1954, **19**, 693.
[11] Hawkins and Elderfield, *ibid.*, 1942, **7**, 573.
[12] Jacobs and Fouché, 16th Congr. Union Pure Appl. Chem., Paris, 1957, Résumés des Comm., Vol. II, p. 316.

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12H-*Indolo*[2,3-a]*quinolizinium Iodide* (V).—(*a*) The iodide (III; R = H, X = I) (0·47 g.), in 5% aqueous acetic acid (50 ml.) with mercuric acetate (1·7 g.), was stirred on the boiling-water bath for 1 hr. After filtration, a sample was diluted and treated with saturated aqueous sodium iodide. The very insoluble precipitate was dissolved in hydrochloric acid and freed from mercury by hydrogen sulphide. The original iodide was then obtained by precipitation with saturated aqueous sodium iodide. Altogether 0·28 g. of starting material was recovered; no trace of dehydrogenated material was found.

(*b*) The dihydro-compound (III; R = H, X = I) (0·15 g.) was finely ground with acid 5% palladium–charcoal [4] (0·3 g.) and rapidly heated to 290° in a Pyrex test-tube and held at this temperature for 5 min. The mixture was cooled and repeatedly extracted with boiling methanol, and the extracts were evaporated; the residue crystallized from absolute ethanol as pale yellow needles (35 mg.), m. p. 304° (decomp.) (Found: C, 52·0; H, 3·1. $C_{15}H_{11}N_2I$ requires C, 52·05; H, 3·2%), $\lambda_{max.}$ in EtOH 2220, 2930, 3430, 3860 Å ($\log_{10}\varepsilon$ 4·69, 4·19, 4·27, 4·13), in 0·01N-alcoholic KOH 2860, 3580, 4360 Å ($\log_{10}\varepsilon$ 4·45, 4·31, 3·56).

6 : 7-*Dihydro*-10-*methoxy*-12H-*indolo*[2,3-a]*quinolizinium Iodide* (III; R = OMe, X = I).—The *m*-methoxyphenylhydrazone of the oxoquinolizinium compound (1·2 g.), when cyclized as described above by anhydrous ethanolic hydrogen chloride (5 hr. at the b. p.), gave the *methoxyindoloquinolizinium iodide* (0·98 g., 83%), crystallizing from absolute ethanol as yellow needles, m. p. 283° (Found: C, 50·95; H, 4·1. $C_{16}H_{14}ON_2I$ requires C, 50·8; H, 4·0%), $\lambda_{max.}$ 2660, 3310, 4240 Å ($\log_{10}\varepsilon$ 3·79, 4·13, 4·28).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*Octahydro*-10-*methoxyindolo*[2,3-a]*quinolizine* (IV; R = OMe).—The methoxyindoloquinolizinium iodide was hydrogenated to completion as described above. The *octahydroindoloquinolizine hydriodide* crystallized from absolute ethanol as pale yellow prisms, m. p. 251—252° (Found: C, 49·3; H, 5·6. $C_{16}H_{21}ON_2I$ requires C, 49·0; H, 5·5%). The *base* (IV; R = OMe) crystallized from aqueous ethanol as colourless prisms, m. p. 201°, $\lambda_{max.}$ 2280, 2690, 2970 Å ($\log_{10}\varepsilon$ 4·58, 3·70, 3·78).

3-*γ*-*Ethoxybutyryl*isoquinoline (VI).—3-Cyano*iso*quinoline [13] (2·8 g.), stirred in dry ether (50 ml.) under nitrogen, was treated with the Grignard reagent from 3-ethoxypropyl bromide (4 g.) in dry ether (40 ml.); a yellow complex was formed. Stirring was continued for 1 hr. and the mixture kept overnight at room temperature. The complex was decomposed with ice-cold 2N-hydrochloric acid, and the ethereal layer separated and extracted with further small portions of acid. The acid extracts were combined and basified with aqueous ammonia (*d* 0·88), and the liberated base was extracted with ether. The ethereal extract was dried ($Na_2SO_4$) and evaporated to dryness. Recrystallization of the solid residue from light petroleum (b. p. 60—80°) gave the *ketone* as colourless prisms, m. p. 74·5° (3·2 g., 72%) (Found: C, 74·35; H, 7·2. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·05%), $\lambda_{max.}$ 2400, 2880, 3120 (infl.), 3250 Å ($\log_{10}\varepsilon$ 4·62, 3·86, 3·61, 3·63).

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxobenzo*[b]*quinolizinium Bromide* (VII).—A solution of the *iso*quinolyl ketone (0·62 g.) in 35% hydrobromic acid (20 ml.) was boiled under reflux for 45 min., then evaporated under reduced pressure. The solid residue was warmed with water and filtered. Treatment of the cooled filtrate with aqueous sodium carbonate and chloroform, as described above, gave a chloroform solution of the bromo-amine which was dried, filtered, and boiled under reflux. The cyclic ketone bromide was rather soluble in chloroform and concentration of the solution to a small volume was necessary before the maximum yield was obtained. Isolated from the chloroform solution, the *bromide* formed colourless plates, m. p. 234° (0·59 g., 83%), unchanged by recrystallization from absolute ethanol, $\lambda_{max.}$ 2570, 3320, 3440 Å ($\log_{10}\varepsilon$ 4·59, 3·73, 3·82). The *picrate*, yellow needles from 95% ethanol, had m. p. 180° (Found: C, 53·3; H, 3·1. $C_{19}H_{14}O_9N_4$ requires C, 53·5; H, 3·3%). The phenylhydrazone bromide crystallized from ethanol as orange-red needles, m. p. 360°. The *phenylhydrazone iodide* crystallized from ethanol as golden needles, m. p. 265—267° (Found: C, 53·0; H, 4·4. $C_{19}H_{18}N_3I,H_2O$ requires C, 52·7; H, 4·65%), $\lambda_{max.}$ 2390, 3980 Å ($\log_{10}\varepsilon$ 4·60, 4·38). The m-*methoxyphenylhydrazone iodide* crystallized from aqueous ethanol as yellow plates, m. p. 262° (decomp.) (Found: C, 53·7; H, 4·2. $C_{20}H_{20}ON_3I$ requires C, 53·9; H, 4·53%), $\lambda_{max.}$ 2400, 3970 Å ($\log_{10}\varepsilon$ 4·60, 4·39).

7 : 8-*Dihydro*-13H-*benz*[g]*indolo*[2,3-a]*quinolizinium Iodide* (VIII; R = R′ = H, X = I).—A solution of the phenylhydrazone bromide (0·34 g.) in anhydrous ethanol (50 ml.) at 0°, was saturated with dry hydrogen chloride, boiled under reflux for 5 hr., then evaporated to dryness

[13] Crowne and Breckenridge, *Canad. J. Chem.*, 1954, **32**, 641.

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under reduced pressure. The solid residue was treated in hot water with aqueous sodium iodide giving a yellow precipitate. The indole iodide (0·3 g., 82%) crystallized from methanol in golden-yellow needles, m. p. 334° (decomp.) [Swan [7] gives 333° (decomp.)], $\lambda_{max.}$ 2380, 2525, 2800, 3520 Å (Swan [7] gives 2390, 2520, 2810, 3520 Å).

The iodide (0·25 g.), ground with acid palladium–charcoal [4] (0·5 g.), was rapidly heated in a Pyrex test tube to 330° (bath-temp.). After 10 min. at 330°, the mixture was cooled and extracted with boiling methanol. The solution showed a green fluorescence, but only unchanged starting material was isolated.

**7 : 8-*Dihydro*-11-*methoxybenz*[g]*indolo*[2,3-a]*quinolizinium Iodide*** (VIII; R = OMe, R′ = H, X = I).—The *m*-methoxyphenylhydrazone iodide (0·38 g.) of the benzoquinolizinium ketone was cyclized under the above conditions with anhydrous ethanolic hydrogen chloride. After recrystallization from methanol, the *indole iodide* formed orange prisms, m. p. 317° (decomp.) (0·32 g., 88%) (Found: C, 56·6; H, 3·9. $C_{20}H_{17}ON_2I$ requires C, 55·1; H, 4·0%), $\lambda_{max.}$ 2410, 3710 Å ($\log_{10}\varepsilon$ 4·56, 4·57).

**5 : 7 : 8 : 13 : 13*b* : 14-*Hexahydro*-11-*methoxybenz*[g]*indolo*[2,3-a]*quinolizine*** (IX; R = OMe). —The methoxybenzindoloquinolizinium iodide was hydrogenated to completion in methanol over Adams catalyst at atmospheric temperature and pressure. The solution was filtered, and during filtration changed from colourless to yellow. Evaporation gave the *hydriodide*, crystallizing as orange needles, m. p. 304° (decomp.), from aqueous methanol (Found: C, 56·15; H, 4·8. $C_{20}H_{21}ON_2I$ requires C, 55·6; H, 4·9%). The *base* (IX; R = OMe) crystallized from aqueous methanol as buff prisms, m. p. 181—182°, $\lambda_{max.}$ 2270, 2670, 2970 Å ($\log_{10}\varepsilon$ 4·61, 3·76, 3·83) in methanol.

We thank the Chemical Society for a grant towards the cost of 2-cyanopyridine.

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KEELE, STAFFORDSHIRE. [*Received, December 9th*, 1957.]

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## 361. N-*Oxides and Related Compounds.*[1] *Part XI.** *Mononitration of 2-, 3-, and 4-Phenyl- and 2- and 4-Benzyl-pyridine 1-Oxide.*

By A. R. HANDS and A. R. KATRITZKY.

The proportions of mononitro-isomers formed from the oxides named in the title have been determined and compared with the data [2,3] for the corresponding pyridines. 2- and 4-Phenylpyridine 1-oxides gave significantly greater proportions of *m*-nitro-compounds than the parent compounds. Substitution in the pyridine oxide ring was never observed. Nitration of 2-phenylpyridine and its oxide in sulphuric acid of varying strengths did not alter the isomer proportions greatly. 2-Phenylpyridine 1-oxide appeared to be nitrated 10—100 times faster than 2-phenylpyridine. It is tentatively concluded that the last two compounds are both nitrated as free base. The results are discussed in terms of differing ease of interaction between a benzene ring and (*a*) an adjacent ring and (*b*) a substituent on an adjacent ring.

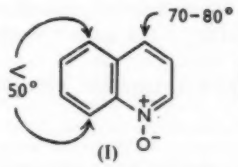
DIPOLE MOMENTS of a series of 4-substituted pyridines and pyridine 1-oxides show [4] that the pyridine 1-oxide ring can create either a deficit or surfeit of electrons at the 4-position, whereas the pyridine ring can create only a deficit; infrared [5] and ultraviolet spectra [6] support this, as do the difficult nitration of pyridines in the 3-position [7] and the easier

* Part X, Katritzky and Monro, *J.*, 1958, 1263.

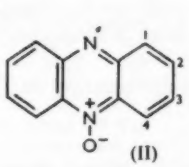
[1] Cf. Katritzky, *Quart. Rev.*, 1956, **10**, 395.
[2] Forsyth and Pyman, *J.*, 1926, 2912.
[3] Bryans and Pyman, *J.*, 1929, 549.
[4] Katritzky, Randall, and Sutton, *J.*, 1957, 1769; Bax, Katritzky, and Sutton, *J.*, 1958, 1254, 1258.
[5] Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, in the press
[6] Katritzky and Monro, unpublished work.
[7] Schofield, *Quart. Rev.*, 1950, **4**, 382.

nitration of pyridine oxides in the 4-position.[1] The strong directing influence is shown by 2- and 3-methoxypyridine 1-oxide, both being nitrated in the 4-position.[8]

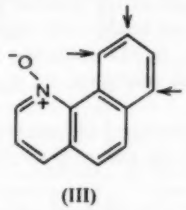
Little is yet known about the transmission of these effects to adjacent rings. Nitration of quinoline 1-oxide is temperature-dependent [cf. (I)].[9] Phenazine 5-oxide (II) on nitration[10] gives 1- and 3-derivatives more quickly than does phenazine, which gives 2(3)-nitrophenazine (however, this may be due to the lower basicity of the oxide; see below), and in the oxide (III) nitration is into the ring furthest from the oxide group.[11]



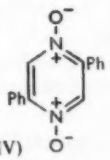
(I)



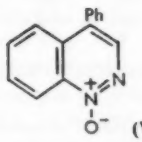
(II)


(III)

As a preliminary to physical measurements, we studied the orientation in the mono-nitration of the mono-phenyl- and -benzyl-pyridine 1-oxides, the behaviour of the corresponding pyridines being known.[2,3] The only related work on *N*-oxides showed that 2 : 5-diphenylpyrazine 1 : 4-dioxide (IV) gave[12] the *mm'*-dinitro-derivative (as did the parent pyrazine[12]) and that 4-phenylcinnoline 1-oxide (V) gave four unoriented nitration products.[13]



(IV)



(V)

The preparation[14] of 2-phenylpyridine gave a little by-product, analysis indicating a pyridyldiphenyl or diphenylpyridine. The m. p. (174°) agreed with that[15] (175°) for a "*p*-pyridylphenylbenzene" (a by-product from the action of benzoyl peroxide on pyridine) (promised evidence for the structure has not been traced). *p*-Diphenylylmagnesium bromide is formed as a by-product from bromobenzene and magnesium,[16] but although our picrate agrees in m. p. with that of 2-*p*-diphenylylpyridine,[17] the latter base has m. p. 141—142°; the ultraviolet data also disagree. The m. p.s exclude 2 : 4- and 2 : 6-diphenylpyridine.

2-, 3-, and 4-Phenyl- and 2- and 4-benzyl-pyridine readily gave 1-oxides (characterised as picrates and picrolonates[18]), which were mononitrated with 1·05 equivs. of nitric acid in hot sulphuric acid. Fractional crystallisation of the product was inefficient. The mixture from the nitration of 2-phenylpyridine showed suitable partition between ethyl acetate and water, but no separation in a 40-tube Craig machine. Dewar's method of ultraviolet spectrophotometry[19] gave only approximate results (in agreement with those finally obtained), doubtless because of small amounts of unknown by-products.

[8] den Hertog, Kolder, and Combé, *Rec. Trav. chim.*, 1951, **70**, 591.
[9] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.
[10] Otomasu, *Pharm. Bull.* (*Japan*), 1954, **2**, 283; 1956, **4**, 117.
[11] Iwai, *J. Pharm. Soc. Japan*, 1951, **71**, 1291.
[12] Beech, *J.*, 1955, 3094.
[13] Atkinson and Simpson, *J.*, 1947, 1649.
[14] Evans and Allen, *Org. Synth.*, 1956, Coll. Vol. II, p. 517.
[15] Overhoff and Tilman, *Rec. Trav. chim.*, 1929, **48**, 993.
[16] Manske and Ladingham, *Canad. J. Res.*, 1949, **27***B*, 158.
[17] Heilbron, Hey, and Lambert, *J.*, 1940, 1279.
[18] Katritzky, *J.*, 1956, 2404.
[19] Dewar and Urch, *J.*, 1957, 345.

XUM

The mixtures from the nitration of 2-, 3-, and 4-phenylpyridine 1-oxide were separated by deoxygenation with phosphorus trichloride, followed by separation of 2-, 3-, and 4-*x*-nitrophenylpyridine.[2] The products' melting points agreed with those given by Forsyth and Pyman;[2] certain of the salts appeared hydrated.

Much 2- and some 4-*p*-nitrobenzylpyridine 1-oxide crystallised from their respective nitration mixtures. Deoxygenation gave tar in the 4-benzyl series; permanganate oxidation of this tar and of the nitration mixture both failed. Successive deoxygenation and oxidation of the residue in the 2-benzyl series gave mixed 2-(nitrobenzoyl)pyridines, on which we could not repeat Bryans and Pyman's separation.[3] 2-*m*-Nitrobenzoylpyridine, m. p. 117°, isolated in low yield by fractional crystallisation, was identical with an authentic specimen, m. p. 117°, from 2-benzoylpyridine. The earlier workers gave[3] m. p. 122°.

The proportions of isomers found are recorded in Table 1, together with data for the nitration of the parent pyridines.

TABLE 1. *Yields (%) of mononitro-compounds in the nitration of phenyl- and benzylpyridines and their 1-oxides.*

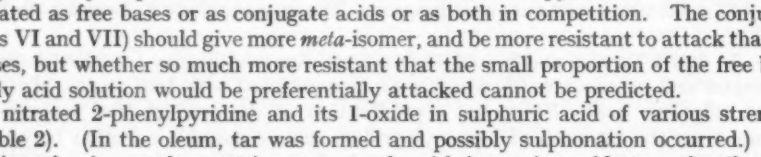
| | Pyridine [a] | | | | Pyridine oxide [b] | | | |
|---|---|---|---|---|---|---|---|---|
| Subst. | *o* | *m* | *p* | Total | *o* | *m* | *p* | Total |
| 2-Ph ..... | 5 | 35 | 42 | 82 | { 0 | 58 | 5 | 63 } |
| | | | | | { 3 | 54 | 7 | 64 } |
| 3-Ph ..... | — | — | 64 | 64 | — | — | 38 | 38 |
| 4-Ph ..... | 13 | 28 | 38 | 79 | 12 | 51 | 13 | 76 |
| 2-$CH_2$Ph ..... | — | 10 | 67 | 77 | — | 2 | 55 | 57 |
| 3-$CH_2$Ph ..... | — | — | 63 | 63 | | Not investigated | | |
| 4-$CH_2$Ph ..... | — | 5 | 70 | 75 | — | — | 9 | 9 |

[a] Refs. 2 and 3. [b] This paper. [c] Duplicate runs.

In 2- and 4-phenylpyridine *para*- is somewhat greater than *meta*-substitution, but in the corresponding 1-oxides *meta*-substitution is much the more important. In the 3-phenyl series, the pyridine undergoes predominant *para*-substitution; *para*-compound was also the only product isolated from the 1-oxide, its yield being lower than from the pyridine, but still more than the *para*-products from the 2- and 4-phenyl oxide. *para*-Substitution predominates for all the benzylpyridines and in 2-benzylpyridine 1-oxide. There is no evidence for substitution into the heterocyclic rings.

*Supplementary Experiments.*—It is unknown whether the pyridines and their oxides are nitrated as free bases or as conjugate acids or as both in competition. The conjugate acids (as VI and VII) should give more *meta*-isomer, and be more resistant to attack than the free bases, but whether so much more resistant that the small proportion of the free bases in highly acid solution would be preferentially attacked cannot be predicted.

We nitrated 2-phenylpyridine and its 1-oxide in sulphuric acid of various strengths (see Table 2). (In the oleum, tar was formed and possibly sulphonation occurred.) The proportion of *m*-isomer does not increase greatly with increasing acid strength; therefore with both 2-phenylpyridine and its 1-oxide the base and conjugate acid are not nitrated significantly in competition.




(VI) (VII) (VIII) (IX)

The metho-salts would presumably behave as the fully protonated compounds. To determine the species reacting, 1-methoxy-2- (VIII) and -4-phenylpyridinium methyl

sulphate were nitrated as before, but the products gave tars with alkali; the action of alkali on 1-methoxypyridinium salts is now known to be complex.[20]

TABLE 2.

| c.c. | $H_2SO_4$ [a] N | $H_0$ [b] | Time (hr.) | B/BH$^+$ [c] | *m* | Product *p* | Total [d] |
|---|---|---|---|---|---|---|---|
| | | | *2-Phenylpyridine* | | | | |
| 15 | 30 | −6·6 | 72 | $10^{-11\cdot6}$ | 31 | 26 | 57 |
| 10 | 37 | −9 | 0·5 | $10^{-14}$ | 31 | 29 | 60 |
| 10 | 45 | ? | 0·5 | ? | 14 | 22 | 36 |
| | | | *2-Phenylpyridine 1-oxide* | | | | |
| 20 | 22 | −6 | 72 | $10^{-7}$ | 45 | 6 | 51 |
| 15 | 30 | −6·6 | 24 | $10^{-7\cdot4}$ | 54 | 11 | 65 |
| 10 | 37 | −9 | 2 | $10^{-10}$ | 49 | 7 | 56 |
| 10 | 45 | ? | 2 | ? | 20 | 5 | 25 |

[a] For $HNO_3$ and substrate see main text. [b] The considerable alterations to $H_0$ made by substrates cannot be estimated but all lie in the same direction. [c] Assumed p$K_a$: 2-phenylpyridine, 5 (cf. pyridine, 5·29; Golumbic and Orchin, *J. Amer. Chem. Soc.*, 1950, **72**, 4145); its oxide, 0·8 (cf. pyridine 1-oxide, 0·79; Jaffe and Doak, *ibid.*, 1955, **77**, 4441). [d] No attempt made to separate the small amounts of *o*-isomer.

Le Fèvre and Mathur reported [21] that 1-methyl-2-phenylquinolinium methyl sulphate gave the *m*-isomer (IX) in 97% yield (calculated on the yield of picrate of m. p. 162—176°, 77% on that of pure picrate of m. p. 181—182°) on nitration with fuming nitric acid at 0°. This indicates that 2-phenylpyridine is nitrated as the free base, in agreement with the tentative conclusion reached below. We failed to nitrate 1-methyl-2-phenylpyridinium methyl sulphate in concentrated sulphuric acid.

A mixture of one equivalent of 2-phenylpyridine and its oxide was treated with one equivalent of nitric acid: the 2-phenylpyridine was largely (74%) recovered. Deoxygenation of the residue, and separation, gave 61% of *m*- and 10% of *p*-nitro-derivative (calc. on $HNO_3$) a ratio which also shows that the oxide was preferentially nitrated. Singly, at least 59% of the 1-oxide was unaffected after 5 min., and at least 65% of the pyridine was nitrated after 40 hr. Therefore the oxide is nitrated *ca.* 10—100 times as fast as the pyridine.

*ortho-para*-Orientation usually occurs together with activation and *meta*-orientation with deactivation; exceptions are substituents (Cl, CH:CH·$CO_2$Et, etc.) electron-withdrawing by inductive and electron-donating by mesomeric effects.[22] No cases are known of *meta*-substitution with activation. If 2-phenylpyridine were being nitrated as its conjugate acid it would follow that changing a substituent involved increased *meta*-substitution with increased activation: therefore 2-phenylpyridine probably is nitrated as such. If this is so, it is unlikely that the less basic 2-phenylpyridine 1-oxide would be nitrated as the conjugate acid; the tentative conclusion is that both compounds react as free bases. The concentration of the oxide free base is *ca.* $10^4$ times that of the pyridine; although the oxide appears to be nitrated some 10—100 times as fast as the pyridine, after allowance for the extent of protonation it reacts at only 0·001—0·01 of the rate for the latter.

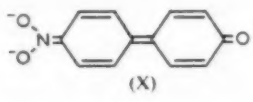
The conclusion that 2-phenylpyridine is nitrated as the free base is unexpected because aniline (of comparable basicity) in excess of concentrated sulphuric acid gives much *m*-nitroaniline [23] by nitration of the cation. The (free) aniline molecule is far more easily substituted electrophilically than the (free) 2-phenylpyridine molecule, and it is hardly to be expected that the 2-phenylpyridine cation would be so much more deactivated than the

[20] Gardner and Katritzky, *J.*, 1957, 4375; Katritzky, unpublished work.
[21] Le Fèvre and Mathur, *J.*, 1930, 2236.
[22] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, Chap. 6.
[23] Hüber, *Annalen*, 1881, **208**, 278.

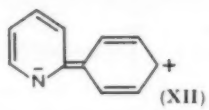
phenylammonium ion as to alter the course of substitution. It is hoped to study these matters further.

An electron-withdrawing group separated from the benzene ring by a vinyl group (as in cinnamic acid, ω-nitrostyrene, 2- and 4-nitrodiphenyl) gives *ortho*- and *para*-nitration.[22] The p$K_a$ of 4-hydroxy-3′- and -4′-nitrodiphenyl and of 4-hydroxydiphenyl itself are similar (9·14, 8·95, 9·40); the anion canonical form (X) is thus not important [24] in the ground state (ultraviolet evidence [25] indicates considerable conjugation).

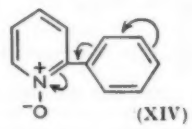
Significantly higher proportions of *para*-isomer isolated in the nitration of 3- than of 2- and 4-phenyl-pyridine and -pyridine oxide (Table 1) indicate that canonical forms of type (XI and XII) *are* important, which is not unexpected for the 2-derivative, as (X) is



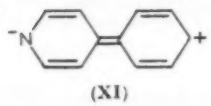
(X)



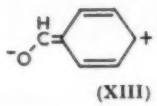
(XII)



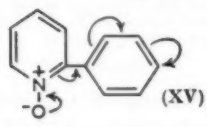
(XIV)



(XI)



(XIII)



(XV)

similar to the important form (XIII) of benzaldehyde. Shifts of type (XIV) are apparently more important than those of type (XV), *i.e.*, the influence of the nitrogen atom in the ring is greater than that of the oxygen atom outside the ring. This may be compared with the greater influence of nitrogen in the ring in 2- and 4-phenylpyridine than of the nitro-group outside the ring in 2- and 4-nitrodiphenyl.

The comparative ease of electron-donation and electron-withdrawal by an *N*-oxide group appears to depend on distance. At very short distances withdrawal appears to predominate, for nitration rarely takes place into the 2-position of a pyridine 1-oxide.[1] Dipole-moments [4] and easy nitration of the corresponding 4-position [1] show that at medium distances the two effects are comparable; the present work indicates that at larger distances electron-withdrawal again predominates. It is hoped to study these effects further by physical methods.

In the benzylpyridines and their 1-oxides, the difference between the rates of nitration of the bases and the conjugate acids would be expected to be smaller than that in the phenyl compounds. Thus the former may be nitrated as conjugate acids. Little difference in behaviour of the pyridine and the corresponding 1-oxide would be expected, and in the 2-series this is so (Table 1).

In the experimental section details are given of preliminary work on the nitration of 2-styryl- and polynitration of 2-phenyl-pyridine 1-oxide. Some 1-methoxypyridinium iodides are also described.

## Experimental

Chloroform extracts were dried over magnesium sulphate.

2-, 3-, and 4-*Phenylpyridine*.—2-Phenylpyridine was prepared [14] in 50% yield. Distillation of the higher-boiling residues gave a *pyridyldiphenyl* (0·2%), plates, m. p. 174° (from methanol) (Found: C, 88·1; H, 5·4; N, 5·8. $C_{17}H_{13}N$ requires C, 88·3; H, 5·7; N, 6·1%), $\lambda_{max.}$ at 270 (ε 26,000) and 286 mμ (ε 28,300) in hexane. The *picrate* formed yellow needles (from ethanol), m. p. 188·5° (Found: C, 60·5; H, 3·7; N, 12·2. $C_{23}H_{16}O_7N_4$ requires C, 60·0; H, 3·5; N, 12·2%). 3- and 4-Phenylpyridine were prepared by known methods (b. p. 136—139°/13 mm. and 77° respectively).

[24] Kreiter, Bonner, and Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 5770.
[25] Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854, and references therein.

2- and 4-Benzylpyridine were redistilled commercial products.

*2- and 4-Benzyl- and 2-, 3-, and 4-Phenyl-pyridine 1-Oxide.*—2-Benzylpyridine (50 g.), 30% aqueous hydrogen peroxide (67 c.c.), and acetic acid (180 c.c.) were kept for 24 hr. at 70—80°; volatile material was removed at 100°/15 mm.; and the residue in hot chloroform (150 c.c.) was digested for 10 min. with potassium carbonate (50 g.). Filtration and evaporation gave *2-benzylpyridine 1-oxide* (51·3 g., 94%), prisms (from benzene), m. p. 100·5° (Found: C, 78·0; H, 6·0; N, 7·5. $C_{12}H_{11}ON$ requires C, 77·8; H, 6·0; N, 7·6%). The *picrate* formed needles (from ethanol), m. p. 119° (Found: C, 52·6; H, 3·6; N, 13·3. $C_{18}H_{14}O_8N_4$ requires C, 52·2; H, 3·4; N, 13·5%). The *picrolonate* formed prisms (from ethanol), m. p. 135·5° (decomp.) (Found: C, 58·5; H, 3·9; N, 15·7. $C_{22}H_{19}O_6N_5$ requires C, 58·8; H, 4·3; N, 15·6%).

The following *pyridine 1-oxides* were similarly prepared: *4-benzyl-* (second treatment with more hydrogen peroxide needed for complete oxidation) (96%), deliquescent prisms (from benzene), m. p. 151° (Found: C, 77·7; H, 5·8; N, 7·5%) [*picrate*, yellow needles (from ethanol), m. p. 94° (Found: C, 52·3; H, 3·4%); *picrolonate*, yellow needles (from ethanol), m. p. 185·5° (Found: C, 58·5; H, 4·2%)]; 2-phenyl- (94%), prisms (from benzene), m. p. 157° (lit.,[26] m. p. 155—155·5°) (by-product formed, see below) [picrate (new *polymorph*), orange prisms (from ethanol), m. p. 130—131° (Found: C, 51·2; H, 3·2. $C_{17}H_{12}O_8N_4$ requires C, 51·0; H, 3·0%) (lit.,[26] yellow prisms, m. p. 150—152°); *picrolonate*, brown rhombs (from ethanol), m. p. 141·5—142° (decomp.) (Found: C, 58·3; H, 4·1; N, 16·5. $C_{21}H_{17}O_6N_5$ requires C, 57·9; H, 3·9; N, 16·1%)]; *3-phenyl-* (90%), needles (from benzene), m. p. 119° (Found: C, 77·6; H, 5·3; N, 8·5. $C_{11}H_9ON$ requires C, 77·2; H, 5·3; N, 8·2%) [*picrate*, needles (from ethanol), m. p. 161° (Found: C, 51·0; H, 3·2; N, 14·2%); *picrolonate*, orange prisms (from ethanol), m. p. 152° (decomp.) (Found: C, 58·2; H, 4·0; N, 16·4%)]; *4-phenyl-* (88%), prisms (from benzene), m. p. 152—152·5°, sublimed at 180°/0·05 mm. (Found: C, 76·9; H, 5·2%) [*picrate*, needles (from ethanol), m. p. 173—173·5° (Found: C, 51·1; H, 3·1%); *picrolonate*, orange prisms (from ethanol), m. p. 205° (Found: C, 57·7; H, 4·1%)].

In the preparation of 2-phenylpyridine 1-oxide, a *by-product*, insoluble in chloroform, formed pale yellow needles (from water or ethanol), m. p. 274° (decomp.) (Found: C, 49·5, 49·7; H, 4·8, 4·8; N, 16·9. $C_7H_5O_3N_2$ requires C, 50·0; H, 4·8; N, 16·7%).

*General Procedures for Mononitration and Deoxygenation of 1-Oxides.—Procedure A.* The oxide (5 g.) was added to a mixture of nitric acid (*d* 1·42; 2·0 c.c., 1·05 mol.) and sulphuric acid (8·5 c.c.) at 0°. The whole was kept for 12 hr. at 100°, poured on ice (20 g.), basified with hydrated sodium carbonate (25 g.), and extracted with chloroform (8 × 75 c.c.). Evaporation of the extracts gave the mixed 2-(nitrophenyl)pyridine 1-oxides.

*Procedure B.* The mixed nitro-oxides (usually *ca.* 5 g.), chloroform (20 c.c.), and phosphorus trichloride (10 c.c.) were kept for 2 hr. at 75°, poured on ice (20 g.), and basified with 2·5N-sodium hydroxide (200 c.c.). The aqueous layer was extracted with chloroform (3 × 50 c.c.) and all the combined organic layers were evaporated to give the mixed nitro-deoxygenated bases.

*Mononitration of 2-Phenylpyridine 1-Oxide.*—The product (from procedures A and B) from the oxide (5 g.), recrystallised from 5N-nitric acid, gave *2-m-nitrophenylpyridine nitrate* (3·47 g.), m. p. 193° (lit.,[2] m. p. 193°). Successive regeneration of the bases (sodium hydroxide solution and chloroform-extraction) and repetition of the above gave two further crops, which, combined and recrystallised from 5N-nitric acid, gave more *m*-isomer nitrate (0·76 g., total yield 54%). Fractional precipitation with aqueous ammonia of the bases remaining gave three crops of *2-p-nitrophenylpyridine*, which after recrystallisation from ethanol had m. p. 130—131° (lit.,[2] m. p. 130·5—131·5°) (0·38 g., 7%) (Found: C, 65·8; H, 3·9; N, 13·9. Calc. for $C_{11}H_8O_2N_2$: C, 66·0; H, 4·0; N, 14·0%). Evaporation of the mother-liquors and repeated recrystallisation from ether gave *2-o-nitrophenylpyridine* (0·20 g., 3%), m. p. 59—60° (lit.,[2] m. p. 60—61°). Aqueous sodium hydroxide and chloroform-extraction of the above nitrate gave *2-m-nitrophenylpyridine* (3·16 g., 54%), m. p. 73° (lit.,[2] m. p. 73—74°) (Found: C, 65·6; H, 4·0; N, 14·1%). In a duplicate run 58% of *m-*, 5% of *p-* but no *o*-isomer were obtained.

*Mononitration of 3-Phenylpyridine 1-Oxide.*—The product from the oxide (3·42 g.) was twice recrystallised from ethanol, to give *3-p-nitrophenylpyridine* (1·52 g., 38%), m. p. 148° (lit.,[2] m. p. 148—149°) (Found: C, 65·9; H, 4·3; N, 13·9%). A brown oil remained.

*Mononitration of 4-Phenylpyridine 1-Oxide.*—The product from the oxide (5·25 g.) was twice recrystallised from 5N-nitric acid, giving *4-m-nitrophenylpyridine nitrate hemihydrate* (total yield

[26] Gilman and Edward, *Canad. J. Chem.*, 1953, **31**, 457.

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4·30 g., 52%), prisms, m. p. 215° (decomp.) [Found (after drying 100°): C, 48·7; H, 3·6. $C_{11}H_9O_5N_3,\frac{1}{2}H_2O$ requires C, 48·5; H, 3·7%] [lit.,[3] m. p. for anhydrous salt 222° (decomp.)].

The bases were regenerated from the mother-liquors and twice crystallised from 5*N*-hydrochloric acid, giving 4-p-*nitrophenylpyridine hydrochloride monohydrate* (total yield, 1·13 g., 13%), needles, m. p. 241—242° [Found (after drying at 100°/14 mm.): C, 51·6; H, 4·7; N, 10·7; Cl, 13·6. $C_{11}H_9O_2N_2Cl,H_2O$ requires C, 51·9; H, 4·4; N, 11·0; Cl, 13·9%].

The base were again regenerated from the mother-liquor and the above process was repeated twice. The bases regenerated from the final mother-liquor gave, with picric acid (1 g.) in ethanol, 4-*o*-nitrophenylpyridine picrate (1·72 g., 13%), m. p. 177° after two recrystallisations from this solvent.

Basification of the above salts and chloroform-extraction gave: 4-*m*- (3·10 g., 51%), m. p. 110° (lit.,[3] m. p. 109—110°) [*picrate*, needles (from ethanol), m. p. 210° (decomp.) (Found: C, 48·0; H, 2·5. $C_{17}H_{11}O_9N_5$ requires C, 47·6; H, 2·6; N, 16·3%)]; 4-*p*- (0·80 g., 13%), m. p. 123° (lit.,[3] m. p. 123—124°) [*picrate*, yellow needles (from ethanol), m. p. 220° (Found: C, 47·4; H, 2·7; N, 16·3%)]; and 4-*o*-nitrophenylpyridine (0·76 g., 12%) (from ether), m. p. 50—52° (lit.,[3] m. p. 51—52°).

*Mononitration of* 2-*Benzylpyridine* 1-*Oxide*.—The oxide (5·5 g.), nitrated by procedure A, gave mixed nitro-derivatives (6·7 g., 98%), m. p. 131—148°. Two recrystallisations from ethanol gave 2-p-*nitrobenzylpyridine* 1-*oxide* (3·71 g., 55%) as needles, m. p. 166·5—167° (Found: C, 62·9; H, 4·5. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4%) [*picrate*, needles (from ethanol), m. p. 134—134·5° (Found: C, 46·8; H, 2·8; N, 14·9. $C_{18}H_{13}O_{10}N_5$ requires C, 47·1; H, 2·8; N, 15·2%)].

Deoxygenation (procedure B) of 2-*p*-nitrobenzylpyridine 1-oxide (1 g.) gave 2-*p*-nitrobenzylpyridine (0·87 g., 94%), m. p. 80° (lit.,[3] m. p. 81°) (Found: C, 67·6; H, 4·9; N, 13·0. Calc. for $C_{12}H_{10}O_2N_2$: C, 67·3; H, 4·7; N, 13·1%). The picrate had m. p. 185—186° (lit.,[3] m. p. 185—187°). 2-*p*-Nitrobenzylpyridine (1 g.), boiled for 1 hr. with aqueous potassium permanganate (1·5 g. in 200 c.c.) and decolorised with sulphur dioxide, gave on cooling 2-*p*-nitrobenzoylpyridine (0·8 g., 52%), m. p. 104° after one recrystallisation from ethanol (lit.,[3] m. p. 105°).

Evaporation of the ethanolic mother-liquors from the 2-*p*-nitrobenzylpyridine 1-oxide, and successive deoxygenation (procedure B) and oxidation (with permanganate as above but product separated with chloroform) of the residue, gave mixed 2-(nitrobenzoyl)pyridines (0·90 g., 13%), m. p. 99—101°. Three recrystallisations from water gave 2-*m*-nitrobenzoylpyridine (0·15 g., 2%), needles, m. p. and mixed m. p. 117° (lit.,[3] needles, m. p. 122°).

2-m-*Nitrobenzoylpyridine*.—Nitric acid (*d* 1·42; 1·8 c.c.) in sulphuric acid (3 c.c.) was added to 2-benzoylpyridine [b. p. 106—110°/0·2 mm. (lit.,[27] b. p. 170—172°/10 mm.); prepared from 2-benzylpyridine [27]] in sulphuric acid (7 c.c.) at 0°. The whole was kept for 1½ hr. at 100°, added to ice (50 g.), and basified with sodium carbonate (23 g.), to give the nitro-derivative (6·5 g., 94%), needles (from ethanol), m. p. 117° unchanged by further recrystallisation (Found: C, 62·9; H, 3·2. Calc. for $C_{12}H_8O_3N_2$: C, 63·2; H, 3·5%).

*Mononitration of* 4-*Benzylpyridine* 1-*Oxide*.—The oxide (5·5 g.), nitrated by procedure A, gave a brown oil. Three recrystallisations from ethyl acetate gave 4-p-*nitrobenzylpyridine* 1-*oxide* (0·63 g., 9%) as prisms, m. p. 165·5—166° (Found: C, 62·2; H, 4·3; N, 11·9. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4; N, 12·2%). The *picrate* formed needles (from ethanol), m. p. 156—156·5° (Found: C, 47·1; H, 2·8. $C_{18}H_{13}O_{10}N_5$ requires C, 47·1; H, 2·8%).

Deoxygenation (procedure B) of the oxide (0·5 g.) gave 4-*p*-nitrobenzylpyridine (0·42 g., 90%), m. p. 74° (lit.,[3] m. p. 74°) (Found: C, 67·2; H, 4·8; N, 12·8. Calc. for $C_{12}H_{10}O_2N_2$: C, 67·3; H, 4·7; N, 13·1%).

Attempted deoxygenation (procedure B) of the total product of nitration gave tar only. Attempted oxidation (permanganate, as above) also failed.

*Nitration in Sulphuric Acid of Various Strengths*.—2-Phenylpyridine (3·10 g.) or 2-phenylpyridine 1-oxide (3·42 g.) was heated at 100° with nitric acid (0·84 c.c.; *d* 1·5) and sulphuric acid. The time of heating and amount and concentration of the sulphuric acid are given in Table 2.

In the 1-oxide experiments the product was isolated and deoxygenated as in procedures A and B. In all experiments the isomers were separated as described above. The proportions of isomers isolated are recorded in Table 2.

[27] Crook and McElvain, *J. Amer. Chem. Soc.*, 1930, **52**, 4006.

*Competitive Nitration of* 2-*Phenylpyridine and its* 1-*Oxide.*—2-Phenylpyridine (3·10 g.) and its oxide (3·42 g.) were added to nitric acid (*d* 1·5; 1·26 g.) in concentrated sulphuric acid (7 c.c.) at 0°. After 5 min., the mixture was heated for 30 min. at 100°, poured on ice (50 g.) and sodium carbonate (20 g.), and steam-distilled. Saturation of the distillate with sodium chloride, extraction with ether, evaporation of the ether, and admixture with picric acid (4 g.) in ethanol gave 2-phenylpyridine picrate (5·47 g., 74%), m. p. and mixed m. p. 175° (lit.,[28] m. p. 175°).

Chloroform-extraction of the residue from the steam-distillation, followed by deoxygenation (procedure B) of the material obtained from the extracts gave mixed 2-nitrophenylpyridines, which were separated by the method given above to give the *m*- (61%) and the *p*-isomer (10%) (calc. on $HNO_3$).

*Nitration of* 2-*Styrylpyridine* 1-*Oxide.*—Nitration of this oxide (5·75 g.) by procedure A and recrystallisation of the product from ethanol gave *x* : *y-dinitro*-2-*styrylpyridine* 1-*oxide* (1·96 g., 23%) as orange prisms, m. p. 195°, or yellow needles, m. p. 193—194° (Found: C, 54·9; H, 3·2; N, 14·5. $C_{13}H_9O_5N_3$ requires C, 54·4; H, 3·1; N, 14·6%).

*Attempted Dinitrations of* 2-*Phenylpyridine* 1-*Oxide.*—The oxide (9 g.) was added to nitric acid (*d* 1·42; 12 c.c.) and sulphuric acid (15 c.c.) at 0°. The whole was kept for 12 hr. at 100°, poured on ice (70 g.), and extracted with chloroform (3 × 100 c.c.). Evaporation of these extracts gave product C (5·7 g.). The aqueous solution, when basified with sodium carbonate (50 g.) and again extracted with chloroform (3 × 100 c.c.), gave (from the chloroform) product D (3·35 g.).

From C, 34-fractional crystallisation from ethanol gave, from the less soluble fractions, x : y-*dinitro*-2-*phenylpyridine* 1-*oxide* (0·1 g., 1%), yellow needles (from ethyl acetate), m. p. 190·5° (Found: C, 50·8; H, 2·8. $C_{11}H_7O_5N_3$ requires C, 50·6; H, 2·7%), and a substance (0·001 g.), yellow plates, insoluble in ethyl acetate, m. p. 189°.

From the more soluble fractions of C, 2-m-*nitrophenylpyridine* 1-*oxide nitrate* (0·12 g., 1%) crystallised as orange prisms, m. p. 154—157° (decomp.) (Found: C, 47·9; H, 3·0. $C_{11}H_9O_6N_3$ requires C, 47·3; H, 3·3%). Basification gave 2-*m*-nitrophenylpyridine 1-oxide, m. p. and mixed m. p. 178° (see below).

From D, 29-fractional crystallisation from water gave, from the less soluble fractions, 2-m-*nitrophenylpyridine* 1-*oxide* (0·78 g., 7%) as pale yellow needles, m. p. 178° (Found: C, 60·9; H, 3·5; N, 13·2. $C_{11}H_8O_3N_2$ requires C, 61·1; H, 3·7; N, 13·0%). The *hemi-picrate* formed prisms (from ethanol), m. p. 151—152° (Found: C, 50·7; H, 2·7; N, 14·3. $C_{11}H_8O_3N_2,\frac{1}{2}C_6H_3O_7N_3$ requires C, 50·8; H, 2·9; N, 14·8%). Deoxygenation (procedure B) of the 1-oxide (0·5 g.) gave 2-*m*-nitrophenylpyridine (0·45 g., 97%), m. p. and mixed m. p. 73°.

From the more soluble fractions of D, 2-p-*nitrophenylpyridine* 1-*oxide* (0·02 g., 0·2%) separated as yellow needles, m. p. 216° (Found: C, 61·3; H, 3·6; N, 12·8%). The *picrate* formed needles (from ethanol), m. p. 162° (Found: C, 46·3; H, 2·6. $C_{17}H_{11}O_{10}N_5$ requires C, 45·8; H, 2·5%). Deoxygenation (procedure B) of the 1-oxide gave 2-*p*-nitrophenylpyridine m. p. and mixed m. p. 130°, identical with the specimen described above.

Oxidation (as above) of 2-*p*-nitrophenylpyridine gave the 1-oxide (77%), m. p. 216°, identical with the specimen described above.

Nitrated with fuming nitric acid, 2-phenylpyridine 1-oxide gave a trace of a x : y : *z-trinitro-derivative*, pale yellow prisms (from ethanol), m. p. 245° (decomp.) (Found: C, 43·2; H, 2·0; N, 18·7. $C_{11}H_6O_7N_4$ requires C, 43·1; H, 2·1; N, 18·3%).

1-*Methoxypyridinium Iodides.*—The following were made by refluxing the oxide with excess of methyl iodide overnight in the dark and evaporating excess of the latter: 1-*methoxy*-4-*phenyl*- (98%), pale yellow needles, deliquescent and light-sensitive, m. p. 99° (decomp.) (Found: C, 46·1; H, 3·7; I, 40·6. $C_{12}H_{12}ONI$ requires C, 46·0; H, 3·9; I, 40·5%); 1-*methoxy*-4-*styryl*- (92%), yellow light-sensitive needles, m. p. 118° (decomp.) (Found: C, 50·1; H, 4·2. $C_{14}H_{14}ONI$ requires C, 49·6; H, 4·2%); and 1-*methoxy-pyridinium iodide* (97%), pale yellow deliquescent needles, rapidly darkening in light, m. p. 90° (decomp.) (Found: C, 31·0; H, 3·5; I, 54·1. $C_6H_8ONI$ requires C, 30·4; H, 3·4; I, 53·6%).

2-Phenylpyridine oxide was recovered unchanged; the products from 2- and 4-benzylpyridine oxide decomposed during their preparation.

4-Phenylpyridine 1-oxide (3·4 g.), heated with dimethyl sulphate (1·9 c.c.) for 12 hr. at 100°, then twice crystallised from ethanol, gave 1-*methoxy*-4-*phenylpyridinium sulphate* (3·92 g., 66%),

[28] Marvel, Brace, Miller, and Johnson, *J. Amer. Chem. Soc.*, 1949, **71**, 34.

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needles, m. p. 100·5° (Found: C, 61·3; H, 5·2; N, 6·0; S, 6·6. $C_{24}H_{26}O_4N_2S$ requires C, 61·5; H, 5·6; N, 6·0; S, 6·8%). The compound gave a precipitate with barium chloride. The product from the 2-analogue was very deliquescent, and was used without characterisation (see above).

This investigation was carried out during the tenure (by A. R. K.) of an I.C.I. Fellowship.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, November 15th*, 1957.]

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## 362. *Potential–*pH *Dependence of the Bismuth Electrode in and out of Contact with Air.*

By H. M. SAMMOUR and A. A. MOUSSA.

The static potential of the bismuth electrode in buffers over almost the whole pH range was investigated. With unprotected electrodes from different sources the potential–pH relation was not a simple linear function over the whole range, and, though consistent with one another, the results could not be readily interpreted in terms of those computed thermodynamically for the presence of any one definite oxide. With protected electrodes, prepared by distilling the hydrogen-reduced metal out of contact with air, the behaviour at pH 11·5—13·0 was in accordance with that of the Bi–$Bi_2O_3$ system, and at pH 9·0—10·5 with that of the Bi–BiO·OH system. At pH 4·0—8·0 an equilibrium involving the metal and $BiO^+$ ions through BiO and BiO·OH as intermediates was assumed to determine the electrodic equilibrium. In the most acid buffers containing chloride ions, and in hydrochloric acid solutions of various concentrations from pH 0·8 to pH 2·8, the behaviour was in accordance with that of the Bi–BiOCl system.

LITTLE is known of the equilibrium (or equilibria) which determines the variation of the static potential of the bismuth electrode with pH. Mehta and Kulkarni,[1] from measurements with massive electrodes over the pH range 5·0—7·4 at 30°, inferred that the suboxide $Bi_2O$ governed the functioning of the electrode as a metal–metal oxide electrode. For the constant $e_0$, *viz.*, potential at unit hydrogen-ion activity, and the coefficient $\partial e/\partial$pH they reported the values 0·4737 v on the normal hydrogen scale and 0·060 v/pH unit respectively. From measurements with various forms of bismuth electrode Schwabe [2] inferred that the potential was a simple linear function of pH from 3 to 14, the corresponding constants being respectively 0·391 v and 0·0507 v/pH unit at 20°. Schwabe and Philipp concluded that the response of the electrode to pH could be explained on the assumption of the existence of $Bi(OH)_3$ on the metal surface.[3] Similar conclusions were reached by Kriventsova and Shatalov,[4] who inferred that in neutral and slightly alkaline solutions the potential was determined by an equilibrium involving the metal and the trioxide while in strongly alkaline ones the metal behaved as a mixture of an oxide and an oxygen electrode.

Previous work on the arsenic and antimony electrodes [5,6] showed that in air they behaved as if governed by an "oxygen overvoltage effect and were legitimately called metal–metal oxide–oxygen electrodes*". From protected electrodes freed previously from the air-formed film such an effect was absent, and the behaviour accorded with that expected from an equilibrium involving the metal and the trioxide.

* *I.e.*, the difference between the potential in air and that computed thermodynamically for one stoicheiometric oxide as found to occur in absence of oxygen.

[1] Mehta and Kulkarni, *J. Indian Inst. Sci.*, 1935, **18**, *A*, 109.
[2] Schwabe, *Z. Elektrochem.*, 1949, **53**, 125.
[3] Schwabe and Philipp, *ibid.*, 1951, **55**, 411.
[4] Kriventsova and Shatalov, *Zhur. fiz. Khim.*, 1953, **27**, 1476.
[5] Tourky and Moussa, *J.*, 1948, 752, 756.
[6] *Idem*, *J.*, 1949, 1297, 1302.

We have now re-examined the behaviour of the bismuth electrode on open circuit in and out of contact with air to discover the extent to which the results can be reconciled with previous ones.

## Experimental

*Electrodes.*—For measurements in air massive and electrodeposited bismuth were used. The first type were of the following qualities: (1) specially prepared bismuth, (2) bismuth from B.D.H., (3) bismuth from Hopkin and Williams, and (4) a Heliger spectrally pure brand; all in the form of cylindrical rods which were carefully abraded with 3/0 emery paper then rubbed against cotton wool. The pure metal was prepared as suggested by Schneider and Myluis [7] by starting with C.P. (chemically pure) bismuth nitrate. Bismuth was electrodeposited (5) on

Fig. 1. *Apparatus for preparation of oxide-free electrodes.*

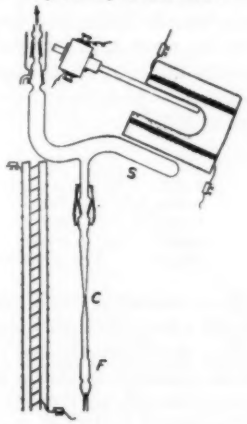
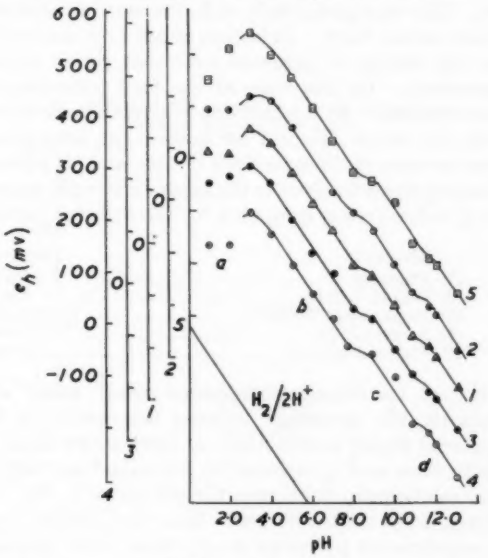



Fig. 2. *Potential–pH curves for unprotected electrodes.*




For key, see text.

copper-coated platinum by the method of Vozdvizhenskii *et al.*,[8] a fresh deposit being used in each measurement.

Oxide- and oxygen-free bismuth for electrodes was prepared by distilling the hydrogen-reduced metal out of contact with air, the device shown in Fig. 1 being used. About 3 g. of the pure metal were heated under purified hydrogen at 600—650° in the silica portion *S* connected to a vacuum line. After four cycles of heating in hydrogen for ½ hr. followed by evacuation, the temperature was raised to 1000—1200°, whereupon the metal started to distil. The fine glittering droplets were received in the electrode jacket *F* which was surrounded with an electric oven at 300°. The distilled metal spread over a very short platinum wire at the bottom of the jacket which served then to maintain electrical contact. Distillation was continued until almost all the metal was transferred (if much was left, the silica tube often cracked on cooling). After thorough evacuation the electrode jacket was sealed at the fine constriction *C*. This was then broken under oxygen-free solution in a cell similar to that described before.[6]

*Solutions.*—For pH 1—10 Clark and Lubs's series of buffer mixtures was used.[9] Buffer

[7] Archibald, "Preparation of Pure Inorganic Compounds," Wiley, New York, 1932, p. 276.
[8] Vozdvizhenskii *et al.*, *Trans. Butlerov Inst. Chem. Tech., Kazan*, 1934, No. 1, 102.
[9] See Clark, "Determination of Hydrogen Ions," Baillere, Tindall, and Cox, London, 3rd edn., 1928, p. 200.

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of pH 10·4 was selected from Kolthoff's series, and for the most alkaline buffers Ringer's mixtures were used; [10] 0·2M-sodium hydroxide solution, pH 13·0, completed the series. Hydrochloric acid solutions were obtained by appropriate dilution of a constant-boiling mixture. All pH values were checked against a hydrogen electrode.

*Measurements.*—These were all carried out at 25° ± 0·1° in an air-bath, and potentials were recorded on an ordinary potentiometer against a saturated calomel half-cell; precautions were taken to avoid the diffusion of chloride ions into the test solution. The potential values cited, however, are on the normal hydrogen scale.

## Results and Discussion

With unprotected electrodes in solutions not freed from dissolved oxygen the static potential recorded 30 min. after immersion remained practically constant during up to 3 hr. This was particularly so in the most alkaline buffers where the maximum difference did not exceed 5 mv. In buffers of pH 4—8, and in the most acid ones containing chloride ions, the change in potential over that period amounted on average to 10 and 15 mv. respectively. On the basis of the final potentials recorded, the plots shown in Fig. 2 were obtained. In no case can the relation be considered a simple linear one over the whole pH range. Except for portion (*a*), corresponding to the most acid buffers, each curve consists of three portions (*b*), (*c*), and (*d*) possessing nearly the theoretical slope and extending respectively over the approximate pH ranges 4·0—8·0, 9·0—10·5, and 11·5—13·0. The $e_0$ values (volts) computed for the different portions were as follows:

| Electrode | Portion (*b*) | (*c*) | (*d*) |
|---|---|---|---|
| (1) Prepared | +0·426 | +0·466 | +0·492 |
| (2) B.D.H. | 0·432 | 0·468 | 0·488 |
| (3) Hopkin and Williams | 0·418 | 0·462 | 0·486 |
| (4) Spectroscopic | 0·420 | 0·466 | 0·486 |
| (5) Electrodeposited | 0·448 | 0·490 | 0·510 |

Except for the electrodeposited metal, which always gave somewhat more positive potentials, the agreement between the results for the various other electrodes may be considered highly satisfactory, so there seems little doubt that the relatively low values of both slope and $e_0$ reported by Schwabe [2] are both due to the assumption that a simple linear relationship holds over the pH range 3—14. The $e_0$ value within portion (*b*) is, on average, some centivolts lower than that, 0·474v, reported by Mehta and Kulkarni [1] for the approximate pH range 5—7; their value approaches that for portion (*c*).

The free energies of formation of the oxides BiO, $Bi_2O_3$, and $Bi_2O_4$ as calculated by Latimer [11] are respectively −43·2, −116, and −109 kcal./mole. From these values, and a metal—metal oxide electrode equilibrium such as (1) being assumed, the corresponding $e_0$ values are 0·292 v, 0·386 v and 0·638 v respectively. The experimental

$$x\mathrm{Bi} + z\mathrm{OH^-} \rightleftharpoons \mathrm{Bi}_x\mathrm{O}_{z/2} + \frac{z}{2}\mathrm{H_2O} + ze \quad . \quad . \quad . \quad . \quad . \quad (1)$$

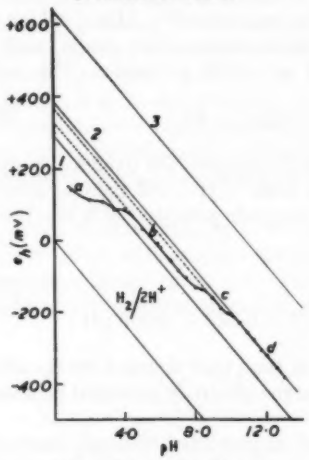
values are higher than that computed for the Bi–BiO system and all of them lie between those for the Bi–$Bi_2O_3$ and the Bi–$Bi_2O_4$ system, so the behaviour of the unprotected electrode cannot be explained simply by assuming that one definite stoicheiometric oxide exists on the surface and governs its functioning as a metal–metal oxide electrode. No free-energy data have been reported for the suboxide $Bi_2O$, but our results with the protected electrode make it unnecessary to consider that this oxide governs the electrode equilibrium (1).

With the protected electrode, prepared by distillation and examined in oxygen-free solutions, the static potentials showed remarkable constancy. During 24 hr., or sometimes 48 hr., the maximum change did not exceed 2—3 mv. The potential–pH curve

[10] Britton, "Hydrogen Ions," Chapman and Hall, London, Vol. I, 1942, p. 311.
[11] See Latimer, "Oxidation Potentials," Prentice-Hall, New York, 1938, p. 115.

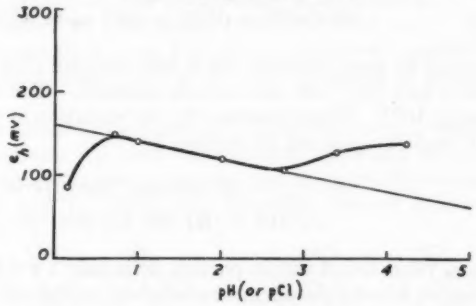
for such an electrode (Fig. 3) shows the same general features as those for the unprotected electrodes; the corresponding portions (*a*), (*b*), (*c*), and (*d*), as well as the transitional pH ranges connecting them are, however, better defined. The curve is shifted bodily towards less positive potentials, $e_0$ corresponding to portions (*b*), (*c*), and (*d*) being 0·335 v, 0·366 v, and 0·389 v respectively. The last value agrees satisfactorily with that computed for the $Bi–Bi_2O_3$ system (0·386 v), which indicates that at pH 11·5—13·0 the trioxide, or the ortho-base $Bi(OH)_3$, is the stable phase in contact with the metal; the hydration energy can be neglected, as shown by Latimer.[11] However, the transformation of the ortho-base to the meta-base BiO·OH is apparently associated with appreciable change in free energy, as can be seen as follows: The solubility of BiO·OH in water was reported by Almkvist[12] to be $5·8 \times 10^{-6}$ mole/l. The value obtained in this laboratory during a study of the amphoteric properties of bismuth oxides was found, however, to be only $2·8 \times 10^{-6}$ mole/l.

FIG. 3. *Potential–pH curves for protected electrodes.*




1, Bi–BiO; 2, $Bi–Bi_2O_3$; 3, $Bi–Bi_2O_4$.

FIG. 4. *Potential–pH curves for a protected electrode in solutions of hydrochloric acid.*




Using our value and assuming complete dissociation into $BiO^+$ and $OH^-$ ions, we find that the free-energy change for the equilibrium (2), as calculated from $\Delta F = -RT \ln K$,

$$BiO·OH \rightleftharpoons BiO^+ + OH^- \quad \ldots\ldots\ldots \quad (2)$$

where $K$ is the solubility product, is 15,150 cal./mole. From this value and taking $\Delta F°$ for $BiO^+$ to be −34,960 cal./mole, as computed from the standard potential value 0·314 v for the half-reaction (3) reported by Smith[13] from direct cell measurements, we find $\Delta F°$ for BiO·OH to be −87,700 cal./mole; the values of $\Delta F°$ used for $OH^-$ and $H_2O$ were those

$$Bi + H_2O = BiO^+ + 2H^+ + 3e \quad \ldots\ldots \quad (3)$$

quoted by Latimer.[11] From the derived free-energy values, $e_0$ for the half-reaction (4)

$$Bi + 2H_2O = BiO·OH + 3H^+ + 3e \quad \ldots\ldots \quad (4)$$

was calculated as 0·369 v, agreeing with that found experimentally to hold within portion (*c*), and thus indicating that the meta-base is the most stable phase in contact with the metal at pH 9·0—10·5.

[11] Almkvist, *Z. anorg. Chem.*, 1908, **103**, 240.
[12] Smith, *J. Amer. Chem. Soc.*, 1923, **45**, 360.

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Before commenting on the $e_0$ value for portion (*b*) for the protected electrode, we consider measurements with this electrode in hydrochloric acid solutions of various concentrations. Fig. 4 shows that static potential plotted as a function of pH (or pCl) of the solutions examined. Over the range 0·8—2·8 the relation is linear, of slope *ca.* −20 mv/pH unit, and the intercept with the ordinate denotes an $e_0$ value of 0·160 v, agreeing with that previously reported by Noyes and Chow [14] for the half-reaction (5). This

$$H_2O + Cl^- + Bi = BiOCl + 2H^+ + 3e \quad . \quad . \quad . \quad . \quad (5)$$

signifies that in pure hydrochloric acid solutions the electrode potential should change by *ca.* 20 mv for a ten-fold change in hydrogen-ion or chloride-ion concentration. We could then ascribe the relatively low potential values registered over the less regular portion (*a*) on the potential–pH curves with both protected and unprotected electrodes to the presence of chloride ions in the most acid members of Clark and Lubs's series of buffers used. The deviation from linearity below pH 0·8, shown in Fig. 4, can be ascribed to the instability of the oxychloride phase due to complex formation.[15] Above pH 2·8 the deviation can be ascribed to the formation of some other intermediate phase, such as oxides or hydroxides. Thus for the equilibrium (6) $\Delta F$ is −4910 cal./mole. This value

$$2BiO{\cdot}OH + 3BiO + 4H^+ \rightleftharpoons 4BiO^+ + H_2O + Bi \quad . \quad . \quad . \quad (6)$$

may not be very accurate, yet it does indicate that in acid solutions the oxides disproportionate into $BiO^+$ ion and metallic bismuth. The ratio $[BiO^+]/[H^+]$ will then be approximately $10^{0\cdot9}$. From reaction (3), the variation of the electrode potential as a function of $BiO^+$ and $H^+$ ions can be written as

$$e = e_0 + (RT/3F) \log [BiO^+][H^+]^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$
$$= 0{\cdot}314 + (RT/3F) \log [BiO^+/H^+][H^+]^3 = 0{\cdot}332 - 0{\cdot}059 \text{ pH}$$

The $e_0$ value found within portion (*b*) is only 3 mv higher than that denoted by the above equation, which thus offers a satisfactory explanation for the electrode potential behaviour within the pH range 4·0—8·0

The similarity in behaviour of both protected and unprotected bismuth electrodes and the corresponding arsenic and antimony electrodes is thus emphasized. Comparison of the $e_0$ values in and out of contact with air shows that, in air, the response of the electrode to pH is governed by an oxygen overvoltage effect, which is inhibited by chloride ions in strong acid solutions. Further, as indicated by the results obtained out of contact with air, the stability of the phases involved in the electrode equilibria over the various pH ranges is compatible with that expected from the amphoteric nature of these phases, as will be reported later.

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[*Received, December 9th*, 1957.]

[14] Noyes and Chow, *ibid.*, 1918, **40**, 739.
[15] Noyes, Hall, and Beattie, *ibid.*, 1917, **39**, 2526.

## 363. *The Constitutions of Geodin and Erdin.*

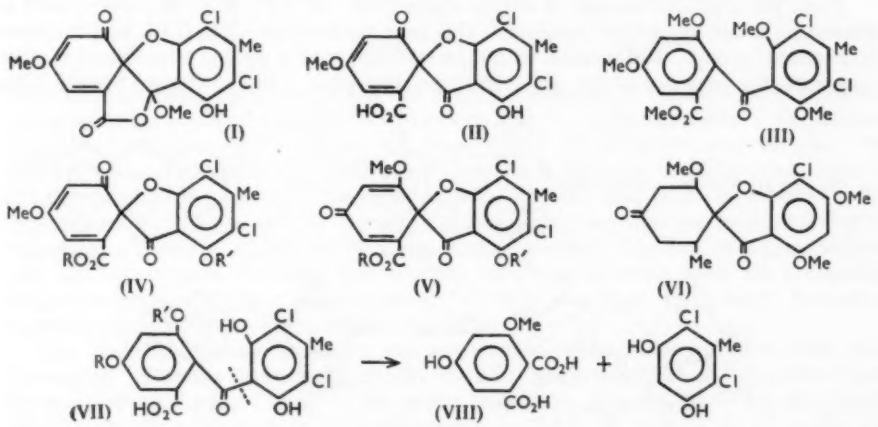
By D. H. R. Barton and A. I. Scott.

(+)-Geodin has been racemised and (±)-erdin resolved to give (+)-erdin. Degradation of dihydroerdin under mild alkaline conditions has been shown to furnish 2 : 6-dichloro-orcinol, 5-hydroxy-3-methoxyphthalic acid, and 2 : 4-dichloro-1 : 6-dihydroxy-3-methoxyxanthone-8-carboxylic acid. On the basis of these and other observations the formulæ proposed earlier for geodin and erdin are modified. The mechanism of the racemisation of (+)-geodin and (+)-erdin is discussed.

The fungal metabolites geodin and erdin were first isolated by Raistrick and Smith [1] from *Aspergillus terreus* Thom. Their chemistry was the subject of elegant and extensive experimentation by Raistrick and his collaborators [1,2,3] which culminated [4] in tentative structural proposals. Disregarding formulæ incompatible with Bredt's rule, they suggested that geodin should be represented as (I) and erdin as (II). The most interesting feature of the chemistry of geodin and erdin is that, whilst the former shows pronounced dextrorotation, the latter is optically inactive. Through the great kindness of Professor H. Raistrick, F.R.S., we have been able to investigate this phenomenon in more detail.

Geodin shows significant infrared bands at 1728, 1665, 1630, and 1610 cm.$^{-1}$. A $\psi$-ester structure such as (I), which should absorb at about 1780 cm.$^{-1}$, is therefore improbable. Additional chemical evidence cited below confirms that the ester grouping of geodin is normal ($CO_2Me$).

Erdin, in agreement with the earlier literature, was optically inactive in several solvents. On treatment with quinine methohydroxide [5] it gave a crystalline salt which with acid afforded optically active (+)-erdin with a rotation similar to that of naturally occurring geodin. The natural (racemic) erdin and (+)-erdin had identical infrared spectra in




solution. Although (+)-erdin was optically stable in neutral solvents, it readily racemised at room temperature in dioxan containing 2% of hydrogen chloride to give back (±)-erdin. In a comparable experiment (+)-geodin furnished for the first time (±)-geodin. (+)- and (±)-Geodin had identical infrared spectra in solution.

[1] Raistrick and Smith, *Biochem. J.*, 1936, **30**, 1315.
[2] Clutterbuck, Koerber, and Raistrick, *ibid.*, 1937, **31**, 1089.
[3] Calam, Clutterbuck, Oxford, and Raistrick, *ibid.*, 1939, **33**, 579.
[4] *Idem, ibid.*, 1947, **41**, 458.
[5] Major and Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368.

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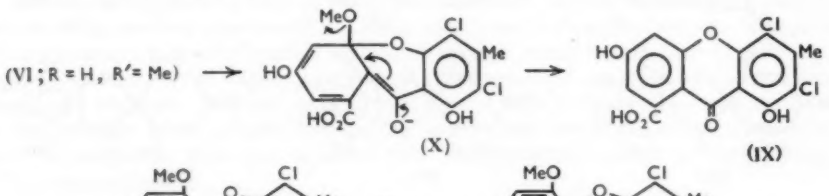
On catalytic hydrogenation (+)-geodin and (±)-erdin readily afford dihydro-derivatives which give identical compounds on complete methylation with diazomethane.[2] The work of Calam, Clutterbuck, Oxford, and Raistrick [3] has shown both by degradation and by synthesis that the methylation product has structure (III). The behaviour on hydrogenation indicates, in agreement with Raistrick and his collaborators,[4] a *cyclo*hexadienone prevented from attaining phenolic aromaticity by one blocking (ethereal) group. One can therefore write formulæ (IV or V; R = Me, R′ = H) for geodin and (IV or V; R = R′ = H) for erdin.

Geodin and erdin show intense ultraviolet absorption at 284 mμ. Å subtraction curve of the spectra of the model compound dihydrogriseofulvin [6] (VI) from that of erdin gave a curve showing $\lambda_{max.}$ 241 mμ (ε 14,000). This is fully consistent with a cross-conjugated dienone such as (V), but not with a linearly extended dienone such as (IV) which would be expected [7] to absorb beyond 300 mμ.

A decisive chemical differentiation between formulæ (IV) and (V) was achieved by degradation of dihydro-derivatives [as (III)]. It was reasoned that cleavage of the bond indicated would be observed in an alkaline degradation of (say) dihydroerdin (VII; R and R′ = Me and H) in which the orcinol ring should behave as a β-diketone system. In the event, treatment of dihydroerdin under mild alkaline conditions gave dichloro-orcinol and 5-hydroxy-3-methoxyphthalic acid (VIII). The structure of dihydroerdin is therefore (VII; R = H, R′ = Me), of erdin is (V; R = R′ = H), and of geodin (V; R = Me, R′ = H). These slight modifications of the formulæ of Calam, Clutterbuck, Oxford, and Raistrick [4] are in agreement with the infrared data. Thus (see above) in the geodin spectrum the band at 1728 cm.$^{-1}$ represents superimposed methoxycarbonyl and *cyclo*pentanone groups, that at 1665 cm.$^{-1}$ the doubly conjugated *cyclo*hexanone, and those at 1630 and 1610 cm.$^{-1}$ carbonyl-conjugated C=C stretching frequencies. In comparison, erdin showed bands at 1717 (broad; carboxyl and *cyclo*pentanone), 1667 (doubly conjugated *cyclo*hexanone), and 1639 and 1610 cm.$^{-1}$ (carbonyl-conjugated C=C).

From the alkaline cleavage of dihydroerdin (VII; R = H, R′ = Me) (see above) an interesting acidic by-product resulted. This gave analyses for $C_{15}H_8O_6Cl_2$ and contained no methoxyl group. Methylation with diazomethane gave a methyl ester dimethyl ether, suggesting the presence of two phenolic hydroxyl groups. The compound showed ultra-



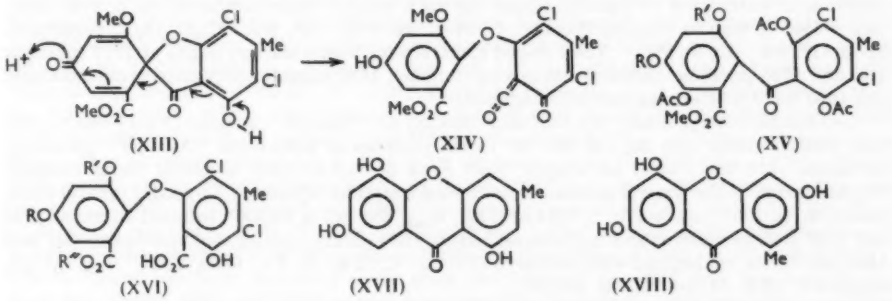

violet and infrared characteristics (see p. 1771) indicative of a xanthone. It must be formulated, therefore, as (IX), being produced as in (X). If this reaction mechanism is accepted, the fact that the xanthone has no methoxyl group confirms the orientation of the methoxyl group in erdin.

The observation that fully methylated dihydroerdin and dihydrogeodin are identical (see above) speaks against a possible *ψ*-ester formula such as (I). Additional chemical

[6] Mulholland, *J.*, 1952, 3987.
[7] *Inter al.*, Dauben and Richards, *J. Amer. Chem. Soc.*, 1956, **78**, 5329; Jeger, Ruegg, and Ruzicka, *Helv. Chim. Acta*, 1947, **30**, 1294; Meisels, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 700.

evidence in favour of a normal ester formulation was secured as follows. Methylation of geodin with diazomethane affords [2] a pyrazoline in agreement with the presence of a reactive ene-1 : 4-dione system. The orientation of diazomethane addition is probably as in formula (XI) for the pyrazoline, since gentle pyrolysis gave a compound whose analysis indicates that it is homogeodin methyl ether (XII). The constitution of the latter was confirmed by its spectroscopic properties (see p. 1771). The pyrazoline from (+)-geodin had identical infrared absorption in solution to that of the pyrazoline from (±)-erdin. In Nujol, however, where differences in crystal lattice may be important, the infrared spectra were different. As expected, the pyrazolines from (+)-geodin and (+)-erdin were identical. Similarly the pyrazolines from (±)-geodin and (±)-erdin were the same compound.

The ready racemisation of (+)-geodin and (+)-erdin, to which reference has been made above, is of theoretical interest since a mechanism must be devised for the inversion of a *quaternary* centre. A clue must be provided by the following observations. Mild acetylation of geodin with sodium acetate and acetic anhydride at room temperature gave a monoacetate (V; R = Me, R′ = Ac), whilst methylation with potassium carbonate and methyl iodide in acetone solution afforded a monomethyl ether (V; R = R′ = Me).




(XIII) (XIV) (XV) (XVI) (XVII) (XVIII)

Both of these compounds were stable to hydrogen chloride in dioxan under conditions which led to the rapid racemisation of (+)-geodin and (+)-erdin (see above). Comparable experiments using acidic methanol are described in the Experimental section. The phenolic hydroxyl group of (+)-geodin and (+)-erdin is therefore involved in some way in the racemisation mechanism. This was confirmed by the fact that (+)-geodin reacted rapidly with pyridine to give an optically inactive adduct whereas the monomethyl ether was stable. A similar adduct was obtained from (±)-erdin. The nature of these adducts was not investigated further. The simplest racemisation mechanism for (+)-geodin would involve [see (XIII)] a keten-ketone (XIV) the reactivity of which might be such as to justify the hypothesis of recyclisation to (±)-geodin.

The modified formulæ for geodin and erdin afford explanations for all relevant prior knowledge. We may mention specifically the acetylation product [3] of (+)-geodin which has structure (XV; R = Ac, R′ = Me) rather than (XV; R = Me, R′ = Ac), and geodin and erdin hydrates [4] which are now formulated as (XVI; R = H, R′ = R″ = Me) and (XVI; R = R″ = H, R′ = Me) respectively. Norgeodin A and B, obtained by treating (+)-geodin with hydriodic acid, are probably to be formulated as (XVII) and (XVIII) respectively.

Recently the isolation of an antibiotic very similar in character to (+)-geodin was reported.[8] Professor H. Raistrick, F.R.S., very kindly forwarded to us a specimen of this substance obtained through the courtesy of Dr. Delmotte-Plaquée. By direct comparison (see p. 1770) we showed that, in spite of an opinion to the contrary,[8] this was simply (+)-geodin and not a new antibiotic.

[8] Delmotte-Plaquée, Delmotte-Plaquée, and Bastin, *J. Pharm. Belg.*, 1956, **11**, 200.

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## Experimental

M. p.s were taken on the Köfler block. Unless specified to the contrary, $[\alpha]_D$ are in $CHCl_3$, ultraviolet absorption spectra in EtOH (taken using the Unicam S.P. 500 Spectrophotometer), and infrared absorption spectra in $CHCl_3$. The latter spectra were kindly determined by Dr. G. Eglinton and his colleagues. Microanalyses were carried out by Mr. J. M. L. Cameron and his associates.

(+)- *and* (±)-*Geodin*.—(+)-Geodin had, after crystallisation from chloroform–ether, m. p. (prisms) 228—231°, $[\alpha]_D$ +140° (*c* 0·80), $\lambda_{max.}$ 284 mμ (ε 19,000). Geodin showed no m. p. depression on admixture with the compound isolated by Delmotte-Plaquéš.[8] The latter had m. p. 227—231°, $[\alpha]_D$ +140° (*c* 1·00), and identical ultraviolet absorption at all wavelengths. The infrared spectra were also identical.

(+)-Geodin (50 mg.) was treated with 2% (w/w) hydrogen chloride in dry dioxan at 25° for 175 min. ($[\alpha]_D$ 0°). Addition of water (2 vols.) afforded a crystalline precipitate (45 mg.) which on further crystallisation from chloroform–ether gave (±)-*geodin* (40 mg.), m. p. (prisms) 225—227°, $[\alpha]_D$ 0° (*c* 2·00), $\lambda_{max.}$ 284 mμ (ε 19,000) (Found: C, 51·55; H, 3·5; OMe, 15·25. $C_{17}H_{12}O_7Cl_2$ requires C, 51·15; H, 3·05; 2OMe, 15·55%). The ultraviolet and infrared spectra of (+)- and (±)-geodin were identical.

(+)-*Geodin Acetate*.—(+)-Geodin (50 mg.) in acetic anhydride (5 ml.) containing fused sodium acetate (20 mg.) was kept at 25° for 16 hr. ($[\alpha]_D$ change from +100° to +128°.) Addition of water gave (+)-*geodin acetate* (50 mg.), needles (from methanol, m. p. 174—175°, $[\alpha]_D$ +180° (*c* 0·40 in dioxan) (Found: C, 51·6; H, 3·75; Ac, 9·5. $C_{19}H_{14}O_9Cl_2$ requires C, 51·75; H, 3·2; Ac, 9·75%). The infrared spectrum (in Nujol) showed bands at 1777 (phenolic acetate), 1735 (methoxycarbonyl and *cyclo*pentanone), 1665 (doubly conjugated *cyclo*hexanone), and 1610 cm.$^{-1}$ (C=C conjugated with carbonyl).

(+)-*Geodin Methyl Ether*.—(+)-Geodin (50 mg.) in " AnalaR " acetone (7 ml.) was treated with methyl iodide (100 mg.) at 60—70° in the presence of anhydrous " AnalaR " potassium carbonate (150 mg.) until an aliquot part gave no colour with alcoholic ferric chloride. Crystallisation of the neutral product from chloroform–ether afforded (+)-geodin methyl ether, plates, m. p. 173°, $[\alpha]_D$ +170° (*c* 0·54 or 0·85), $\lambda_{max.}$ 280 mμ (ε 16,600), infrared bands at 1735 and 1720 (*cyclo*pentanone and methoxycarbonyl), 1660 (doubly conjugated *cyclo*hexanone), and 1605 cm.$^{-1}$ (C=C conjugated with carbonyl) (Found: C, 52·6; H, 3·1; OMe, 22·25. $C_{18}H_{14}O_7Cl_2$ requires C, 52·3; H, 3·4; 3OMe, 22·55%).

(+)- *and* (±)-*Erdin*.—(±)-Erdin, crystallised from chloroform–methanol, had m. p. (needles) 210—212°, $[\alpha]_D$ 0° (*c* 1·00 or 2·00 in $CHCl_3$; or *c* 1·20 in dioxan), $\lambda_{max.}$ 284 mμ (ε 21,000).

(±)-Erdin (1·08 g.) in ethanol (15 ml.) was treated with 0·35N-aqueous quinine metho-hydroxide[5] (7·65 ml., 1 equiv.). The solvents were removed *in vacuo* and the residual bright yellow oil taken up in ethanol (15 ml.) with addition of dioxan (120 ml.). The crystalline salt (deposited during 16 hr.) was recrystallised five times from ether–ethanol, to give (+)-erdin quinine metho-salt (1·18 g.), yellow prisms, m. p. 193°, $[\alpha]_D$ −94° (*c* 0·70 in EtOH). This was acidified with 10% w/w sulphuric acid (40 ml.) with shaking in the presence of ether. Recovery from the ether gave (+)-*erdin* (400 mg.). Recrystallised from chloroform–light petroleum this (250 mg.) had m. p. (prisms) 210—212°, $[\alpha]_D$ +149° (*c* 0·41 in dioxan) (Found: C, 49·3; H, 2·8; Cl, 18·35; OMe, 8·55. $C_{16}H_{10}O_7Cl_2$ requires C, 49·9; H, 2·6; Cl, 18·4; OMe, 8·05%). (+)-Erdin showed absorption identical with that of (±)-erdin in both the ultraviolet and the infrared region. Treatment of (+)-erdin (5 mg.) with 2% hydrogen chloride in dioxan as for (+)-geodin gave back (±)-erdin, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ 0° (*c* 0·50)}.

Treatment of (±)-erdin with aqueous sulphuric acid as previously described[4] gave the known erdin hydrate, m. p. (from aqueous methanol) 218—219°, $\lambda_{max.}$ 217 and 317 mμ (ε 45,000 and 8000 respectively). The spectrum is comparable with that [$\lambda_{max.}$ 316 mμ (ε 6000)] recorded by Ungnade[9] for 2-carboxy-3-hydroxydiphenyl ether.

*Action of Diazomethane on Geodin and Erdin*.—(a) (+)-*Geodin*. Treatment with ethereal diazomethane[2] gave the known pyrazoline, m. p. 149—151° (decomp.), $[\alpha]_D$ −49° (*c* 1·00 in $C_6H_6$), −69° (*c* 0·65 in $CHCl_3$).

(b) (±)-*Geodin*. Similar treatment afforded the racemic pyrazoline, identical in m. p., mixed m. p., and infrared spectrum (in Nujol) with the derivative of (±)-erdin (see below).

(c) (±)-*Erdin*. Similar treatment furnished the known[2] racemic pyrazoline, m. p. 152—153° (decomp.), $[\alpha]_D$ 0° (*c* 1·10 in $C_6H_6$). The infrared spectra of the racemic and optically

[9] Ungnade, *J. Org. Chem.*, 1951, **16**, 1318.

active pyrazolines were identical in $CHCl_3$ but differed significantly, especially in the "fingerprint" region, in Nujol. The ultraviolet absorption spectra were identical, showing $\lambda_{max.}$ 270 mμ (ε 18,000).

(+)-*Erdin*. Similar treatment gave the optically active pyrazoline, identical in m. p., mixed m. p., rotation {$[\alpha]_D$ −45° (*c* 0·70 in $C_6H_6$), −68° (*c* 0·51 in $CHCl_3$)}, and infrared spectrum (in Nujol) with the pyrazoline from (+)-geodin.

*Pyrolysis of the Pyrazoline from* (±)-*Erdin*.—The pyrazoline (50 mg.) was heated at 155—160° for 2 min. (copious gas evolution). Crystallization from ether afforded (±)-*homogeodin methyl ether*, prisms, m. p. 178—180°, $\lambda_{max.}$ 278 mμ (ε 19,200) (Found: C, 53·6; H, 4·1; *C*-Me, 4·05. $C_{18}H_{14}O_7Cl_2$ requires C, 53·4; H, 3·8; 1*C*-Me, 3·5%).

*Dihydrogeodin and Dihydroerdin*.—Dihydrogeodin, prepared according to Raistrick and Smith,[1] had m. p. 216—218°, $[\alpha]_D$ 0° (*c* 2·00), $\lambda_{max.}$ 279 mμ (ε 20,000), 320 mμ (ε 22,000 in 0·01N-NaOH), 295 mμ (ε 21,000 in 0·01N-potassium carbonate). Dihydroerdin, prepared similarly, had m. p. 230—232°, $\lambda_{max.}$ 285 mμ (ε 16,000), 320 mμ (ε 22,200 in 0·01N-NaOH).

*Action of Alkali on Dihydroerdin*.—Dihydroerdin (420 mg.) in N-sodium hydroxide (40 ml.) was heated on the steam-bath for 2 hr. under nitrogen. The solution was then saturated with carbon dioxide at 5° and the phenolic fraction removed by ether-extraction. Sublimation of the latter at 80°/1 mm. afforded 2 : 6-dichloro-orcinol (60—80 mg.), identified by m. p. and mixed m. p.

The acid fraction was separated into ether-soluble and water-soluble acids. After removal, by fractional crystallisation from ethanol, of some dihydroerdin, the former fraction gave 2 : 4-*dichloro*-1 : 6-*dihydroxy*-3-*methylxanthone*-8-*carboxylic acid*, bright yellow needles (from ethanol), m. p. 330—335°, $\lambda_{max.}$ 240, 274, 314, and 360 mμ (ε 38,000, 11,000, 17,000, and 6000 respectively) (Found: C, 50·35; H, 3·05; Cl, 19·4; OMe, 0. $C_{15}H_8O_6Cl_2$ requires C, 50·7; H, 2·3; Cl, 19·95, 0%). The infrared spectrum showed bands at 1690 (carbonyl), 1605 (hydrogen-bonded xanthone-carbonyl) and 1580 cm.$^{-1}$ (aromatic C=C). Treatment in methylene dichloride with diazomethane for 2 days gave the *methyl ester dimethyl ether*. From chloroform–methanol this formed yellow prisms, m. p. 230—232°, $\lambda_{max.}$ 243, 280 (shoulder), 305, and 340 mμ (ε 37,600, 11,400, 11,400, and 6300 respectively) (Found: C, 54·9; H, 3·75; OMe, 23·0. $C_{18}H_{14}O_6Cl_2$ requires C, 54·5; H, 3·35; 3OMe, 23·4%). The infrared spectrum showed bands at 1730 (methoxycarbonyl), 1660 (xanthone-carbonyl), and 1610 and 1585 cm.$^{-1}$ (aromatic C=C). The spectra of xanthone, measured at the same time, showed $\lambda_{max.}$ 243, 263, 288, and 333 mμ (ε 37,600, 18,000, 5000, and 6100) as well as infrared bands at 1660, 1610, and 1585 cm.$^{-1}$ (see above).

The water-soluble acid fraction was obtained from the aqueous phase (see above) by saturation with ammonium sulphate followed by continuous ether-extraction. Purification by sublimation (twice) at 160°/$10^{-2}$ mm. gave 5-*hydroxy*-3-*methoxyphthalic anhydride* (50 mg.), m. p. 230° (Found: C, 56·1; H, 3·7; OMe, 15·5. $C_9H_6O_5$ requires C, 55·7; H, 3·1; OMe, 15·9%). The compound gave no colour with ferric chloride. Treatment with ethereal diazomethane followed by refluxing for 2 hr. in N-sodium hydroxide and sublimation of the resultant acid furnished 3 : 5-dimethoxyphthalic anhydride, m. p. and mixed m. p. 148—149° (sublimes at 130°) (with an authentic specimen of the same m. p. prepared according to Birkinshaw and Bracken's directions [10]).

3-*Hydroxy*-5-*methoxyphthalic Anhydride*.—5-Hydroxy-3-methoxybenzoic acid [11] was converted into the oily methyl ester by dissolution in methanol containing a trace of sulphuric acid. This oil (5·5 g.) in ether (50 ml.) was aded to a stirred suspension of zinc cyanide (7·5 g.) in ether (100 ml.) at 0—5° and the mixture saturated with dry hydrogen chloride. Decantation and dissolution of the residual aldimine hydrochloride in hot water (10 ml.) gave on ether-extraction the crude aldehyde. This was dried and treated with potassium hydroxide (5 g.) and water (1·0 ml.) at 190° for 30 min. (nickel crucible). Dissolution in water, acidification with dilute sulphuric acid, saturation with ammonium sulphate, and extraction into ether afforded 3-hydroxy-5-methoxyphthalic acid, m. p. (from ethyl acetate–light petroleum) 185—190° (decomp.), giving a red colour with ferric chloride. For this compound Nikuni [12] recorded m. p. 177—179°.

The acid was heated at 180—190° for 15 min. and the product then sublimed at

[10] Birkinshaw and Bracken, *J.*, 1942, 308.
[11] Mauthner, *J. prakt. Chem.*, 1927, **116**, 315.
[12] Nikuni, *Bull. Agric. Chem. Soc. Japan*, 1942, **18**, 41; *Chem. Abs.*, 1951, **45**, 5140.

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180°/$10^{-4}$ mm., to furnish *3-hydroxy-5-methoxyphthalic anhydride* as prisms, m. p. 232—234° (sublimes at 180° and upwards) (Found: C, 55·15; H, 3·5. $C_9H_6O_5$ requires C, 55·7; H, 3·1%).

| Compound | Solvent system | Time after dissolution (in min.) with (in parentheses) $[\alpha]_D^\circ$ |
|---|---|---|
| (+)-Erdin | 2% (w/w) HCl in dioxan | 2 (+130), 25 (+82), 55 (+38), 175 (±0) |
| (+)-Geodin | 2% (w/w) HCl in dioxan | 2 (+103), 25 (+60), 55 (+28), 175 (±0) |
| | 2% (w/w) HCl in dry MeOH | 2 (±0) |
| | 0·2% (w/w) HCl in dry MeOH | 2 (+70), 10 (+50), 30 (+22), 105 (+1) |
| | 0·2% (w/w) $CH_2Cl{\cdot}CO_2H$ in dry MeOH | 2 (+119), 30 (+115), 24 × 60 (+100), 168 × 60 (+50), 240 × 60 (+25) |
| | Pyridine | 2 (+120), 100 (+20), 190 (±0) |
| (+)-Geodin methyl ether | 2% (w/w) HCl in dioxan | 2 (+137), 140 (+137) |
| | 2% (w/w) HCl in dry MeOH | 2 (+80), 20 (+40), 40 (+10) |
| | 0·2% (w/w) HCl in dry MeOH | 2 (+100), 15 (+95), 35 (+80), 185 (+30) |
| | 0·2% (w/w) $CH_2Cl{\cdot}CO_2H$ in dry MeOH | 2 (+146), 60 (+146), 19 × 60 (+146), 67 × 60 (+146) |
| | Pyridine | 2 (+173), 170 (+173), 960 (+173) |
| (+)-Geodin acetate | 2% (w/w) HCl in dioxan | 2 (+180), 55 (+177), 205 (+177) |
| (+)-Geodin pyrazoline derivative | Pyridine | 2 (−55·5), 25 (−55·5), 180 (−55·5) |

The compound gave no immediate colour with ferric chloride; it was depressed in m. p. by 15° on admixture with 5-hydroxy-3-methoxyphthalic anhydride (see above). Treatment with ethereal diazomethane followed by alkaline hydrolysis, etc., as in the cognate preparation above, gave 3 : 5-dimethoxyphthalic anhydride (m. p. and mixed m. p.).

*Racemisation Experiments.*—The Table shows rates of loss of optical activity in the solvent systems indicated in all cases at 25° at a concentration of approximately 0·5 w/v %.

The products from the action of hydrogen chloride in dioxan on (+)-erdin and (+)-geodin have been described above. That (+)-geodin acetate and methyl ether were unaffected under these conditions was confirmed by recovery of the starting materials. The action of pyridine on (+)-geodin afforded, on dilution with water, an *adduct*. Recrystallised from chloroform–methanol this had m. p. (orange-yellow needles) 320°, $[\alpha]_D$ ±0°, $\lambda_{max.}$ 245 and 370 mμ (ε 40,000 and 21,400), infrared max. at 1726, 1625, 1612, 1585, and 1535 $cm.^{-1}$ (Found: C, 55·4; H, 4·4; N, 3·1; OMe, 12·6. $C_{22}H_{17}O_7Cl_2N$ requires C, 55·25; H, 3·6; N, 2·95; 2OMe, 13·0%). Treated under the same conditions (±)-erdin gave a comparable *adduct*, m. p. (yellow needles from pyridine) >330° (Found: C, 53·6; H, 3·2; N, 3·15. $C_{21}H_{15}O_7Cl_2N$ requires C, 54·3; H, 3·3; N, 3·0%). (+)-Geodin methyl ether and (+)-geodin pyrazoline were recovered unchanged from dissolution in pyridine.

The experiments in methanol were followed spectrophotometrically with the appropriate controls. In all experiments in this solvent where racemisation occurred, the initial $\lambda_{max.}$ at 284 mμ (ε *ca.* 19,000) was replaced by a peak of lower intensity at 317—319 mμ (ε 6000 to 9000 depending on the degree of completion of the reaction). The latter band corresponds to the diphenyl ether chromophore of erdin hydrate (see above). Treatment of (±)-erdin (25 mg.) with 2% methanolic hydrogen chloride as above afforded *erdin hydrate dimethyl ester methyl ether* (15 mg.) as prisms (from aqueous ethanol or methanol), m. p. 140—142°, $\lambda_{max.}$ 317 mμ (ε 9000), infrared max. (in Nujol) at 1708 and 1660 $cm.^{-1}$ (unbonded and hydrogen-bonded $CO_2Me$), insoluble in aqueous sodium hydrogen carbonate, soluble in aqueous sodium hydroxide, and giving a violet ferric colour very similar to that of methyl salicylate (Found: C, 51·25, 51·3; H, 3·90, 3·75; OMe, 27·9. $C_{19}H_{18}O_8Cl_2$ requires C, 51·25; H, 4·1; 4OMe, 27·9%). The same compound was obtained on treatment of (+)-geodin in the same way. This ester (6 mg.) with ethereal diazomethane, when worked up in the usual way, gave erdin hydrate dimethyl ester [4] dimethyl ether (3 mg.). From the ferric reaction mentioned above and the infrared indication of a hydrogen-bonded methoxycarbonyl group, this dimethyl ester dimethyl ether must have the phenolic hydroxyl in the dichloro-orcinol ring.

We are especially grateful to Professor H. Raistrick, F.R.S., for the specimens of (+)-geodin and (±)-erdin and for his interest, helpful comments, and encouragement. We thank the Government Grants Committee of the Royal Society and Imperial Chemical Industries Limited for financial assistance. This work was carried out by one of us (A. I. S.) during the tenure of an I.C.I. Fellowship from the University of Glasgow.

THE UNIVERSITY, GLASGOW, W.2. [*Received, December 19th,* 1957.]

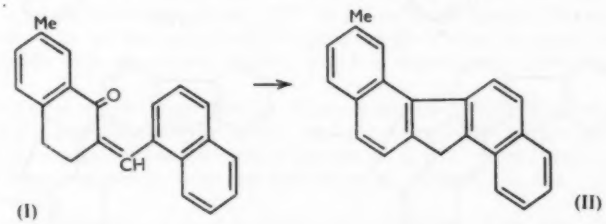
## 364. *Some New Polycyclic Derivatives of Fluorene and Carbazole.*

By G. Saint-Ruf, Ng. Ph. Buu-Hoï, and P. Jacquignon.

For biological assay as potential carcinogens or tumour-inhibitors, new condensed hydrocarbons derived from fluorene were synthesised by cyclodehydration of the appropriate arylidene-1-tetralones, and new polycyclic derivatives of carbazole were prepared *via* the phenylhydrazones of the appropriate tetralones.

Condensed polycyclic derivatives of fluorene, such as 1 : 2-5 : 6-dibenzofluorene,[1] and of carbazole, such as the mono-[2] and di-benzocarbazoles,[3] are of biological interest as carcinogens and as inhibitors of tumour growth. In order to determine the effect of methyl groups or further rings on these properties, various new compounds in both series have been synthesised.

No homologue of 1 : 2-5 : 6-dibenzofluorene was hitherto known, and the 2″-methyl derivative (II) has now been prepared by cyclodehydration of 1 : 2 : 3 : 4-tetrahydro-7-methyl-2-1′-naphthylidene-1-oxonaphthalene (I) with phosphoric oxide.[4] Like 1 : 2-5 : 6-




(I) (II)

dibenzofluorene, compound (II) gave a dipicrate. Among more highly condensed hydrocarbons, the compound (IV) was obtained by cyclodehydration of ketone (III), prepared by condensation of acenaphthene-5-aldehyde with 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene. Another heptacyclic hydrocarbon (VI), isomeric with (IV) but having an anthracene arrangement, was obtained from ketone (V), itself prepared by condensing 1-naphthaldehyde with 7 : 8 : 9 : 10-tetrahydro-7-oxoaceanthrene.[5] It is interesting that this hydrocarbon can also be considered as a naphtho-derivative of the carcinogenic 7 : 8-*cyclo*pentadienoaceanthrene;[6] the presence of the aceanthrene group was apparent from the yellow colour of the hydrocarbon and the dark colour of its dipicrate [the isomer (IV) gave a monopicrate].

In the carbazole group,[4] acenaphtheno(4′ : 3′-1 : 2)carbazole (VIII) was obtained by chloranil dehydrogenation[7] of the corresponding dihydro-derivative (VII), prepared by Fischer indolisation of the phenylhydrazone of 7 : 8 : 9 : 10-tetrahydro-10-oxoaceanthrene; similarly, pyreno(4′ : 3′-1 : 2)carbazole (X) was prepared from the dihydro-derivative

[1] Badger, Cook, Hewett, Kennaway, Kennaway, Martin, and Robinson, *Proc. Roy. Soc.*, 1940, *B*, **129**, 439; Badger, Elson, Haddow, Hewett, and Robinson, *ibid.*, 1942, *B*, **130**, 255.
[2] Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. Biol.*, 1947, **141**, 635; Schürch and Winterstein, *Z. physiol. Chem.*, 1935, **236**, 79.
[3] Boyland and Brues, *Proc. Roy. Soc.*, 1937, *B*, **122**, 429.
[4] Cf. Buu-Hoï and Cagniant, *Rev. sci.*, 1942, **80**, 319, 384, 436; *ibid.*, 1943, **81**, 30; Buu-Hoï and Saint-Ruf, *J.*, 1957, 3806.
[5] Fieser and Peters, *J. Amer. Chem. Soc.*, 1932, **54**, 4373.
[6] Shear and Leiter, *J. Nat. Cancer Inst.*, 1951, **2**, 99.
[7] Cf. Barclay and Campbell, *J.*, 1945, 530; Buu-Hoï *et al.*, *J. Org. Chem.*, 1949, **14**, 492, 802; 1950, **15**, 131, 511, 957.

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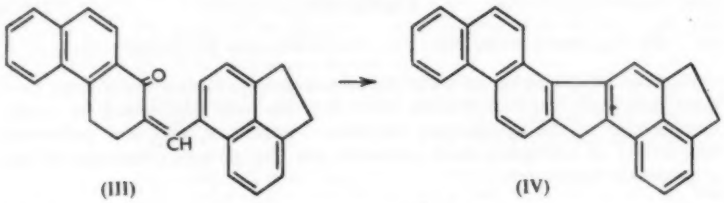
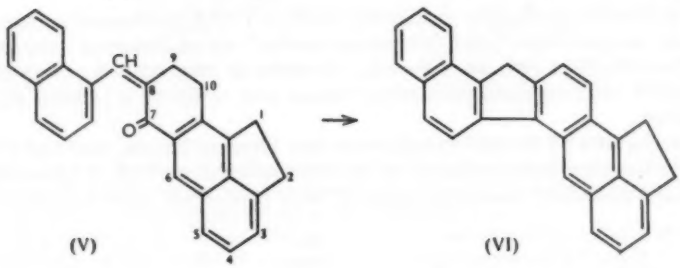
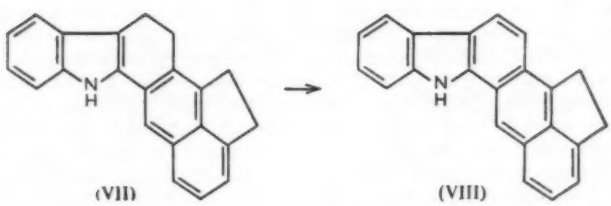
(IX), obtained from the phenylhydrazone of 1′ : 2′ : 3′ : 4′-tetrahydro-4′-oxo-3 : 4-benzopyrene. This last carbazole carries the molecular arrangement of the highly carcinogenic 3 : 4-benzopyrene, which accounts for its intense yellow colour; both the condensed



(III) (IV)

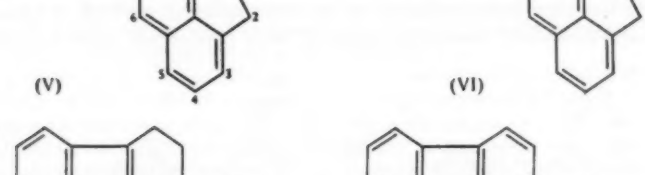


(V) (VI)



(VII) (VIII)

carbazoles (VIII) and (X) share with carbazole itself the property of forming stable, deeply coloured molecular complexes with tetrachlorophthalic anhydride.[8]



(IX) (X)

All the new compounds reported are undergoing tests in this Institute for carcinogenic and tumour-inhibitory effects.

## Experimental

**1 : 2 : 3 : 4-*Tetrahydro*-7-*methyl*-2-1′-*naphthylidene*-1-*oxonaphthalene*** (I).—1 : 2 : 3 : 4-Tetrahydro-7-methyl-1-oxonaphthalene [9] (10 g.) and freshly redistilled 1-naphthaldehyde (11 g.) were shaken, at room temperature, with 4% ethanolic potassium hydroxide (50 c.c.) and left overnight. The bulky precipitate formed was filtered off, washed with dilute aqueous acetic acid, then with water, and recrystallised twice from ethanol, giving the *product* as leaflets (18 g.),

[8] Buu-Hoï and Jacquignon, *Compt. rend.*, 1952, **234**, 1056; *Bull. Soc. chim. France*, 1957, 488; *Experientia*, 1957, **13**, 375.

[9] Ruzicka and Mörgeli, *Helv. Chim. Acta*, 1936, **19**, 377; Fieser and Dunn, *J. Amer. Chem. Soc.*, 1936, **58**, 572.

m. p. 139°, dissolving in sulphuric acid with a cherry-red halochromy (Found: C, 88·8; H, 5·8. $C_{22}H_{18}O$ requires C, 88·6; H, 6·1%).

*2''-Methyl-1 : 2-5 : 6-dibenzofluorene* (II).—A solution of the foregoing ketone (15 g.) in dry xylene (75 c.c.) was refluxed with finely powdered phosphoric oxide (14 g.) for 24 hr. After cooling, ice was added, the xylene layer washed with dilute aqueous sodium hydroxide, then with water, and dried ($Na_2SO_4$), the solvent removed, and the residue fractionated *in vacuo*. The portion, b. p. 255—265°/1 mm., solidified on trituration with ethanol, and recrystallised from ethanol–benzene as needles (2·5 g.), m. p. 179° (Found: C, 94·2; H, 5·6. $C_{22}H_{16}$ requires C, 94·3; H, 5·7%). This *hydrocarbon* gave a *dipicrate*, brick-red prisms, m. p. 157°, from ethanol (Found: N, 11·9. $C_{34}H_{22}O_{14}N_6$ requires N, 11·4%).

*2-Acenaphthen-5'-ylidene-1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene* (III).—A mixture of 1 : 2 : 3 : 4-tetrahydro-1-oxophenanthrene [10] (4·2 g.) and acenaphthene-5-aldehyde (4 g.; prepared by the dimethylformamide technique [11]) was treated with 4% ethanolic potassium hydroxide (50 c.c.) as above; the condensation *product* formed yellow needles (5 g.), m. p. 196°, from ethanol–benzene, giving a violet-red halochromy with sulphuric acid (Found: C, 89·7; H, 5·5. $C_{27}H_{20}O$ requires C, 90·0; H, 5·6%).

*1 : 2-Benzo-3 : 4'-cyclopentenonaphtho(2'' : 1''-5 : 6)fluorene* (IV).—The cyclisation *product*, b. p. 262—267°/0·1 mm., obtained by 30 hours' refluxing of the foregoing ketone (4 g.) in xylene (50 c.c.) with phosphoric oxide (3·2 g.), crystallised as colourless leaflets (1·5 g.), m. p. 251°, from benzene (Found: C, 94·6; H, 5·8. $C_{27}H_{16}$ requires C, 94·7; H, 5·3%). The *picrate* formed brownish needles, m. p. 230°, from benzene (Found: N, 7·6. $C_{33}H_{21}O_7N_3$ requires N, 7·4%).

*7 : 8 : 9 : 10-Tetrahydro-7-oxoaceanthrene.*—This ketone, m. p. 145°, was prepared by heating a solution of γ-3-acenaphthenylbutyric acid [5] (9 g.) in dry benzene (150 c.c.) with thionyl chloride (6 g.) for 1 hr. on the water-bath, evaporating the solvent *in vacuo*, and cyclising the crude acid chloride with aluminium chloride (6 g.) in nitrobenzene (100 c.c.) at room temperature.

*7 : 8 : 9 : 10-Tetrahydro-8-1'-naphthylidene-7-oxoaceanthrene* (V).—Prepared from the foregoing ketone (2 g.), 1-naphthaldehyde (1·5 g.), and 4% ethanolic potassium hydroxide (50 c.c.), this *ketone* (3·2 g.) crystallised as pale yellow prisms, m. p. 212°, from ethanol–benzene, giving a deep violet halochromy with sulphuric acid (Found: C, 89·8; H, 5·8. $C_{27}H_{20}O$ requires C, 90·0; H, 5·6%).

*7 : 8-Benzoacenaphtheno(3' : 4'-3 : 4)fluorene* (VI).—Prepared from the foregoing ketone (3 g.) and phosphoric oxide (2·4 g.) in xylene (75 c.c.), this *hydrocarbon* (1 g.) crystallised as bright yellow leaflets, m. p. 265°, from ethanol–benzene (Found: C, 94·5; H, 5·3. $C_{27}H_{16}$ requires C, 94·7; H, 5·3%). The *dipicrate* formed almost black needles, m. p. 178°, from benzene (Found: N, 10·8. $C_{39}H_{24}O_{14}N_6$ requires N, 10·5%).

*3 : 4-Dihydroacenaphtheno(4' : 3'-1 : 2)carbazole* (VII).—A mixture of 7 : 8 : 9 : 10 tetrahydro-7-oxoaceanthrene (1 g.) and phenylhydrazine (1 g.) was heated at 120° until steam ceased to be evolved, and the crude phenylhydrazone thus obtained was treated with a boiling solution of hydrogen chloride in glacial acetic acid (10 c.c.). After dilution with water, the cyclisation product which was precipitated was washed with water, dried, and recrystallised twice from *cyclo*hexane, giving almost colourless prisms (1 g.), m. p. 206°; the solution in benzene showed a strong violet fluorescence (Found: C, 99·2; H, 5·8. $C_{22}H_{17}N$ requires C, 89·5; H, 5·8%). This *carbazole* gave with an equimolar amount of tetrachlorophthalic anhydride in acetic acid, an addition compound as red needles, m. p. 224° (decomp.).

*Acenaphtheno(4' : 3'-1 : 2)carbazole* (VIII).—The foregoing dihydro-compound (0·7 g.) and chloranil (2·5 g.) in dry xylene (50 c.c.) were refluxed for 2 hr.; after cooling, the precipitated tetrachloroquinol was filtered off, the xylene solution washed several times with aqueous sodium hydroxide, then with water, and dried ($Na_2SO_4$), and the solvent distilled *in vacuo*. Crystallisation of the solid residue from benzene gave the *carbazole* as pale yellow prisms (0·5 g.), m. p. >340° (brown-violet halochromy with sulphuric acid) (Found: N, 4·8. $C_{22}H_{15}N$ requires N, 4·8%). The molecular complex with tetrachlorophthalic anhydride formed brown needles, decomp. >230°. This carbazole is isomeric with the known acenaphtheno(4' : 5'-1 : 2)-carbazole.[12]

*3 : 4-Dihydropyreno(4' : 3'-1 : 2)carbazole* (IX).—The crude phenylhydrazone made from

[10] Haworth, *J.*, 1932, 1125.
[11] Cf. Saint-Ruf, Buu-Hoï, and Jacquignon, *J.*, 1958, 48.
[12] Buu-Hoï, Khôi, and Xuong, *J. Org. Chem.*, 1951, **16**, 315.

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1′ : 2′ : 3′ : 4′-tetrahydro-4′-oxo-3 : 4-benzopyrene [11] (1·5 g.) and phenylhydrazine (1·5 g.) gave with hydrogen chloride in acetic acid (20 c.c.) in the usual way the *dihydro-compound* which crystallised as yellowish prisms (2 g.), m. p. 158°, from acetic acid (mauve halochromy with sulphuric acid) (Found: C, 90·6; H, 5·2; N, 4·2. $C_{24}H_{17}N$ requires C, 90·9; H, 5·0; N, 4·1%). The picrate formed violet needles, m. p. 172°, from benzene.

*Pyreno*(4′ : 3′-1 : 2)*carbazole* (X).—Prepared from the above dihydro-compound (0·8 g.) and chloranil (2 g.) in xylene (50 c.c.), this *carbazole* formed deep yellow needles, which showed no definite m. p. below 285° and charred above that temperature (Found: C, 91·1; H, 4·5; N, 4·2. $C_{24}H_{15}N$ requires C, 91·5; H, 4·4; N, 4·1%); the halochromy with sulphuric acid was deep violet, and the addition compound with tetrachlorophthalic anhydride was orange.

This investigation was supported in part by a research grant from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service; the authors thank the authorities concerned.

THE RADIUM INSTITUTE, THE UNIVERSITY OF PARIS. [*Received, December 23rd*, 1957.]

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## 365. *The Mechanism of the Coupling of Diazonium Salts with Heterocyclic Compounds. Part III.* Indazole.*

By R. D. BROWN, B. A. W. COLLER, and (in part) M. L. HEFFERNAN.

The mechanism of the coupling of diazonium compounds with indazole has been studied by determining the variation in the rate of coupling with diazosulphanilic acid over the pH range 8·5—10·1. The results indicate that the reaction involves only the small proportion of anion in equilibrium with the neutral indazole molecule in these solutions.

The observed orientations for various electrophilic substitutions in indazole are briefly reviewed in the light of the mechanism now established.

Some kinetic evidence suggests that the azo-compound formed initially in this reaction undergoes a further reaction with another molecule of the diazonium compound.

OUR previous investigations of the coupling mechanism with heterocycles containing a secondary nitrogen atom in a five-membered ring have shown that sometimes the neutral molecule is involved [1] and sometimes the anion obtained by ionization of the proton from the secondary nitrogen atom.[2] These observations clarify apparent anomalies for the orientation of electrophilic substitutions since the orientation expected for the neutral molecule may differ from that in the anion.[3,4] In the case of indazole the observed orientations suggest that in electrophilic substitutions different forms of indazole are involved in different cases because nitration occurs at the 5-position,[5] while diazo-coupling [6] and iodination in alkaline solution [7] yield 3-substituted indazoles. Since the last two reactions involve alkaline solutions while nitration occurs in acidic media, the implication is that the former result from substitution in the indazole anion and the latter in the neutral molecule or cation. We have now established this for diazonium coupling by determining the manner in which the rate of reaction varies with the pH of the solution.

* Part II, *J.*, 1957, 2398.

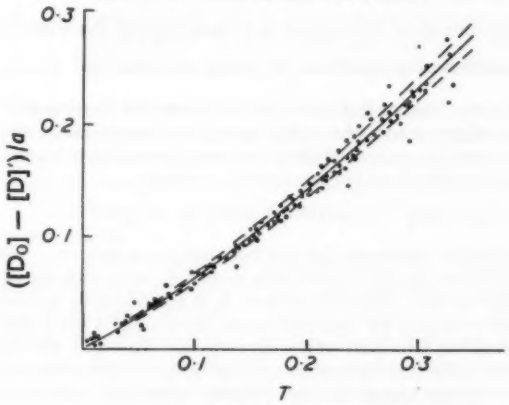
[1] Binks and Ridd, *J.*, 1957, 2398.
[2] Brown, Duffin, Maynard, and Ridd, *J.*, 1953, 3937.
[3] Bassett, Brown, and Penfold, *Chem. and Ind.*, 1956, 892.
[4] Brown and Heffernan, *J.*, 1956, 4288.
[5] von Auwers and Kleiner, *J. prakt. Chem.*, 1928, **118**, 75.
[6] Bamberger and von Goldberger, *Annalen*, 1899, **305**, 350.
[7] von Auwers and Lohr, *J. prakt. Chem.*, 1924, **108**, 297.

## Experimental

Indazole (L. Light & Co.) was recrystallized from water and from ligroin (b. p. 60—80°) to constant m. p. 147° (corr.). Sulphanilic acid, sodium nitrite, and buffer reagents were of " AnalaR " quality. The R-acid was B.D.H. purified sodium salt. Buffer solutions were made from appropriate quantities of borax, boric acid, or carbon dioxide-free sodium hydroxide solution; the concentrations were adjusted to produce an ionic strength of 0·05. Kinetic runs were performed substantially as described in Part I [2] except that the reaction was stopped by running 5 ml. aliquot parts into a mixture of 25 ml. of saturated borax and 1·0 ml. of 1·0% R-acid sodium salt solution, and in the diazotization hydrobromic acid was used in place of hydrochloric acid plus sodium bromide.

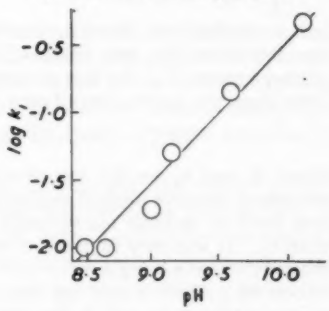
A Hilger Spekker colorimeter was used to determine the concentration of azo-compound produced by the coupling of unchanged diazosulphanilic acid and the R-acid. The " infinity " readings were always small but proportional corrections were applied.

Fig. 1. *Variation of $k_1$ with* pH *at* 25°.




*Top line*: $k_1 = 0{\cdot}052$, $k_2 = 6$.
*Middle line*: $k_1 = 0{\cdot}050$, $k_2 = 6$.
*Bottom line*: $k_1 = 0{\cdot}050$, $k_2 = 5$.

Fig. 2. *Determination of $k_1$ and $k_2$ from kinetic data at* pH 9·15.




*Evaluation of Reaction Rate Constants.*—Runs performed with a large excess of indazole gave appreciable deviations from first-order kinetics. This was initially suspected to be due to concurrent diazonium decomposition which for a variety of diazonium compounds shows [8] considerable deviations from first-order kinetics at higher pH values. However, decomposition of diazosulphanilic acid solutions was too slow to be responsible for the observed deviations. The deviations were found to depend upon the indazole concentration and it was then found possible to account for the observed kinetic curves in terms of two consecutive second-order steps involving the diazonium compound, together with a slow concurrent diazonium decomposition. It is tempting to assume a second coupling of the diazosulphanilic acid with the monoazo-compound first formed because the latter is an anion owing to the presence of the sulphonate group and so may be sufficiently reactive to undergo a rapid second coupling. We have not so far isolated such a bisazo-compound from the reaction mixtures but we hope to investigate this further.

The rate constants for the two steps were evaluated by a modification of Wideqvist's method.[9, 10] In this a correction is first determined for the concurrent diazonium decomposition. Under the conditions of our experiments the initial stages of the decomposition followed very nearly zero-order kinetics. The zero-order rate constants used for correcting for decomposition are given in Table 1. The rates could not be made completely reproducible and the uncertainty

[8] Brown and Penfold, unpublished results.
[9] Wideqvist, *Arkiv Kemi*, 1955, **8**, 545.
[10] Brown and Coller, *Austral. J. Chem.*, 1958, **11**, 90.

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in the listed values may be as great as 50%. However, this has little effect on the determination of the rates of coupling since the decomposition corresponds to only a small correction term.

TABLE 1. *Decomposition of diazosulphanilic acid at 25°.*

| | | | | | | |
|---|---|---|---|---|---|---|
| Initial concn. $\times 10^4$ | 2·0 | 20·0 | 20·0 | 2·0 | 2·0 | 2·0 |
| pH | 8·50 | 8·65 | 9·00 | 9·15 | 9·60 | 10·10 |
| $k_0$ (mole l.$^{-1}$ sec.$^{-1}$ $\times 10^{10}$) | 6 | 90 | 200 | 50 | 100 | 250 |

TABLE 2. *Coupling of diazosulphanilic acid with indazole at 25°.*

| | | | | | | |
|---|---|---|---|---|---|---|
| $10^4[D]_0$ | 2·0 | 20·0 | 20·0 | 2·0 | 2·0 | 2·0 |
| No. of runs | 3 | 3 | 6 | 11 | 4 | 3 |
| Range of $a \times 10^3$ | 5·4—8·1 | 7·1—11·4 | 1·7—11·9 | 1·6—8·1 | 2·9—5·1 | 2·1—5·1 |
| pH | 8·50 | 8·65 | 9·00 | 9·15 | 9·60 | 10·10 |
| $10^3k_1$ (l. mole$^{-1}$ sec.$^{-1}$) | 1·0 ± 0·1 | 1·0 ± 0·05 | 1·8 ± 0·2 | 5·0 ± 0·2 | 14·0 ± 1·0 | 46·0 ± 1·0 |
| $k_2$ (l. mole$^{-1}$ sec.$^{-1}$) | 8 ± 3 | 5 ± 2 | 5 | 6 ± 1 | 7 ± 1 | 8 ± 1 |

From each value of the diazonium concentration determined in a coupling run the variable $T = \int_0^t ([D]_0 - [D])dt$ was evaluated by numerical integration, [D] being the observed diazonium concentration. Next an amount $k_0t$ was subtracted from [D] to obtain the "corrected" concentration [D]′, and $([D]_0 - [D]')/a$, where $a$ was the initial indazole concentration, was plotted against $T$. By this procedure it can be shown [9, 10] that for two consecutive second-order steps the points from all runs at a given pH fall on the same curve, namely:

$$([D]_0 - [D]')/a = [2(k_1 - k_2) + (2k_2 - k_1)e^{-k_1T} - k_1e^{-k_2T}]/(k_1 - k_2)$$

where $k_1$ and $k_2$ are the second-order velocity constants for the consecutive reactions. The statistical iterative method suggested by Wideqvist for determining $k_1$ and $k_2$ from such curves was found to oscillate too violently be convenient, probably because $k_2$ is considerably greater than $k_1$. It was easy to find the two rate constants by trial and error, the fitting of the earlier part of the curve being sensitive to $k_1$ and of the later part of the curve to $k_2$. In Fig. 1 the line of best fit (judged by eye) and two curves illustrating variations corresponding to our estimated uncertainties in $k_1$ and $k_2$ are shown. Values found for the velocity constants, and their estimated uncertainties, are given in Table 2.

*Discussion of Results.*—The graph of log $k_1$ against pH is shown in Fig. 2, a line of slope unity being included with the experimental points. The line of best fit found by a weighted least-squares procedure with the points weighted in inverse ratio to the estimated uncertainty in log $k_1$ has a slope of 1·09 with 95% confidence limits of ±0·2. Therefore within our limits of accuracy the experimental data conform to the equation

$$-d[D]/dt = k[OH^-][HIn][D]$$

where $[OH^-]$ is the actual concentration of hydroxyl ion and [HIn] and [D] represent analytical concentrations of indazole and diazosulphanilic acid respectively. Since [11] the p$K_a$ of the diazonium cation is about 11 and the p$K_a$ of indazole is probably considerably greater, the experimental results agree with either of the following two mechanisms: (i) DOH + HIn ⟶ Products, or (ii) $D^+ + In^-$ ⟶ Products. It is now accepted that diazonium coupling involves electrophilic attack by the diazonium cation, not by the diazohydroxide or diazoate [12] and so scheme (i) must be rejected in favour of (ii). It therefore follows that the heterocycle reacts by way of the small equilibrium proportion of anion present in solution.

The observed orientation in the coupling reaction is thus indicative of the relative reactivities of the various ring positions in the anion rather than in the free base. The preferential attack of the 3-position is in agreement with qualitative molecular-orbital

[11] Wistar and Bartlett, *J. Amer. Chem. Soc.*, 1941, **63**, 413.
[12] Zollinger, *Chem. Rev.*, 1952, **51**, 347.

predictions with the assumption that both tertiary nitrogen atoms are *less* electronegative than the ring carbon atoms.[3]

The authors gratefully acknowledge a grant from the Research Fund of the Chemical Society. One of them (M. L. H.) is indebted to the C.S.I.R.O. for the award of a studentship.

UNIVERSITY OF MELBOURNE, CARLTON, N.3,
VICTORIA, AUSTRALIA. [*Received, November 4th*, 1957.]

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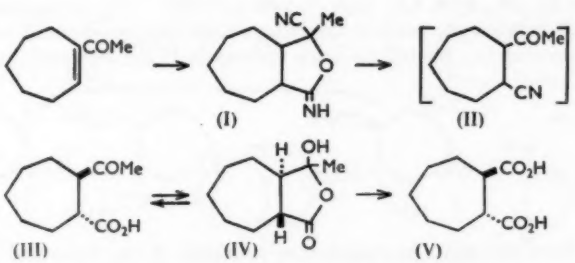
## 366. trans-cyclo*Heptane*-1 : 2-*dicarboxylic Acid and its Conversion into* trans-bicyclo[5 : 3 : 0]*Decan*-9-*one*.

By D. C. AYRES and R. A. RAPHAEL.

*cyclo*Heptane-1 : 2-dicarboxylic acid has been obtained from *cyclo*heptanone. Resolution by brucine has shown it to possess the *trans*-configuration and an independent stereospecific synthesis has been effected. Elaboration of the acid has produced *trans-bicyclo*[5 : 3 : 0]decan-9-one, obtained earlier by a sterically equivocal route.

IT has been shown [1] that the catalytic and " chemical " reduction of *bicyclo*[5 : 3 : 0]dec-7-en-9-one lead stereoselectively to the two possible stereoisomers of *bicyclo*[5 : 3 : 0]decan-9-one, but no unambiguous assignment of configuration could be deduced. The key reference compounds for this task are the hitherto unknown *cis*- and *trans-cyclo*heptane-1 : 2-dicarboxylic acids and methods for the synthesis of the two acids were accordingly investigated.

As methods which were successful in the *cyclo*pentane and *cyclo*hexane series [2] proved abortive when applied to the corresponding *cyclo*heptane derivatives, a new method of approach was devised. *cyclo*Heptanone was converted into 1-ethynyl*cyclo*heptanol [3] which was transformed by the Meyer–Schuster rearrangement into acetyl*cyclo*heptene by Newman's technique.[4] The latter ketone with cold aqueous-alcoholic potassium cyanide furnished a crystalline substance, whose formula $C_{11}H_{16}ON_2$ corresponded to the




(Only one enantiomorph is shown throughout.)

cyanohydrin of the expected cyano-ketone (II); similar behaviour has been reported for mesityl oxide.[5] The infrared characteristics of the product, however, indicated that a simple cyanohydrin structure was unlikely. No C≡N stretching frequency was present but bands appeared in the carbonyl region at 1710 and 1735 cm.$^{-1}$. A possible structure

[1] Islam and Raphael, *J.*, 1955, 3151.
[2] Raphael in Rodd's " Chemistry of Carbon Compounds," Elsevier, London, Vol. IIA, pp. 111, 235.
[3] Heilbron, Jones, Toogood, and Weedon, *J.*, 1949, 1827.
[4] Newman, *J. Amer. Chem. Soc.*, 1953, **75**, 4740.
[5] Lapworth, *J.*, 1904, **85**, 1214.

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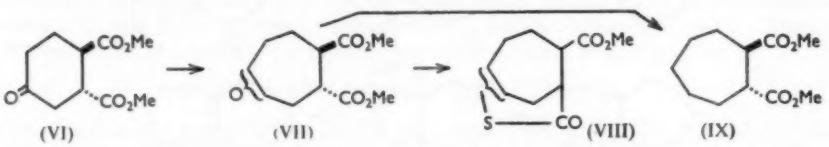
which corresponds to these findings is (I), in which the cyano- and the acetimidoyloxy-group are attached to the same carbon atom, so that the absence of the C≡N frequency may be rationalised since the band is absent in similar compounds with cyano- and acetoxy-groups on the same carbon atom.[6] Although higher in frequency than expected, the absorption in the carbonyl region may be regarded as the C=N stretching frequency of the imine. From results described in the sequel the rings in structure (I) are probably *trans*-fused.

Alkaline hydrolysis of compound (I) yielded the keto-acid (III), presumably by way of the cyano-ketone (II). The infrared spectrum (in $CCl_4$) of this acid showed it to be in equilibrium with the lactol (IV), with a band at 1780 cm.$^{-1}$ (γ-lactone): for the solid state (Nujol dispersion) a normal bonded-hydroxyl band appeared at 3300 cm.$^{-1}$, indicating a substantial proportion of the lactol.[7] With diazomethane the keto-acid yielded the normal ester corresponding to (III), while esterification[8] with methanol produced a mixture of this ester and the pseudo-ester corresponding to (IV). This mixture showed an absorption band at 1773 cm.$^{-1}$ (γ-lactone) in addition to the expected keto-ester bands at 1710 and 1727 cm.$^{-1}$. Both the pure normal ester and the ester mixture gave the 2 : 4-dinitrophenylhydrazone of the normal ester, the yield from the mixture being about 70%, which is presumably the content of normal ester in the mixture.

For large-scale working a substantially one-step conversion of acetyl*cyclo*heptene into the keto-acid (III) was devised, using aqueous glycol as solvent. Treatment of the acid with sodium hypochlorite[9] gave a homogeneous crystalline *cyclo*heptane-1 : 2-dicarboxylic acid (V) in an overall yield of 73% from *cyclo*heptanone. This product was shown to be the racemic *trans*-isomer by its resolution into two dibrucine salts. The less soluble salt crystallised from ethyl acetate; the more soluble one was purified by fractional precipitation from ethanol solution by ether. Regeneration of the free acids gave the two enantiomorphs of *trans-cyclo*heptane-1 : 2-dicarboxylic acid, m. p. 138—142°, $[\alpha]_D^{18}$ +3·3° (±0·3°), and m. p. 138—141°, $[\alpha]_D^{19}$ −4·7° (±0·5°). Although optically stable in ethanol solution over considerable periods both acids were racemised to a considerable extent by crystallisation from benzene or benzene–light petroleum. A *trans*-structure for the acid (V) is also in agreement with the dissociation constants. A potentiometric titration, kindly carried out by Dr. J. C. Speakman, showed the thermodynamic dissociation constants at 20° to be $pK_1$ 4·30, $pK_2$ 6·16, *i.e.*, $\Delta pK = 1{\cdot}86$ (±0·03). The corresponding differences for the *trans*-1 : 2-dicarboxylic acids in the *cyclo*pentane and *cyclo*hexane series are $\Delta pK$ = 1·95 and 1·75 respectively; for the *cis*-acids the values[10] are 2·14 and 2·40.



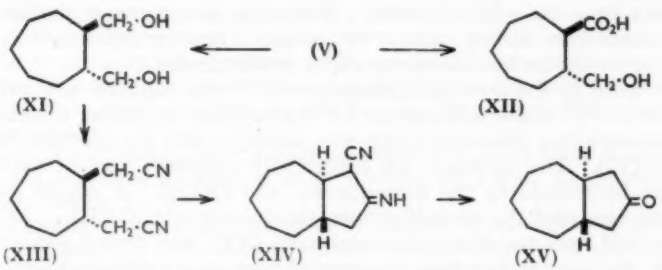

Further, we have effected a stereoselective synthesis of the *trans*-acid (V). Dimethyl 4-oxo*cyclo*hexane-*trans*-1 : 2-dicarboxylate (VI) was prepared by a Diels–Alder reaction involving 2-ethoxybuta-1 : 3-diene and fumaroyl chloride, followed by treatment of the crude product with dry methanol. The hydrogen chloride liberated in the latter reaction was neutralised with solid sodium hydrogen carbonate, and one of two products was obtained depending on the speed of this operation. Gradual addition of the alkali allowed hydrolysis of the intermediate enol ether to the crystalline free keto-diester (VI); rapid addition gave a product containing some of this ester (VI) but consisting mainly of the

[6] Kitson and Griffith, *Analyt. Chem.*, 1952, **24**, 334.
[7] Grove and Willis, *J.*, 1951, 879.
[8] Clinton and Laskowski, *J. Amer. Chem. Soc.*, 1948, **70**, 3135.
[9] Smith, Prichard, and Spillane, *Org. Synth., Coll. Vol.* III, 1955, p. 302.
[10] Speakman, *J.*, 1941, 491.

corresponding dimethyl ketal. The keto-diester and the ketal show similar absorption at 1740 cm.$^{-1}$ but in the ketal an additional triplet appears at 1169, 1127, 1096 cm.$^{-1}$ characteristic of this function.[11] Alkaline hydrolysis of the keto-diester (VI) gave the crystalline *trans*-diketo-acid, m. p. 188°, from which the ester was regenerated by diazomethane. A keto-diacid of this structure, but with m. p. 161°, was prepared by Newman and Lloyd [12] by alkaline hydrolysis of the adduct from 2-methoxybutadiene and maleic anhydride. As their compound gave *trans-cyclo*hexane-1 : 2-dicarboxylic acid by Huang-Minlon reduction,[13] the American authors assigned the *trans*-structure to their keto-diacid. In view of the discrepant melting points, however, it is highly probable that Newman and Lloyd's acid is the *cis*-isomer, inversion having taken place during the drastic alkaline treatment entailed in Huang-Minlon reduction.

The keto-diester (VI) with diazomethane generated *in situ* from methylnitrosourethane gave a mixture of the required dimethyl *trans-cyclo*heptanone-1 : 2-dicarboxylate (VII) and unchanged starting material. The latter was removed by selective treatment with semicarbazide acetate in methanol; crystallisation then yielded the ester (VII), m. p. 60—64°. This product was probably a mixture of the theoretically possible 4- and 5-keto-compounds, with one of them predominating. Reaction of the product (VII) with ethanethiol followed by treatment of the crude thioketal with Raney nickel [14] gave as sole product a sulphur-containing liquid of formula $C_{10}H_{14}O_3S$. When ethanedithiol was used the predominant product was the same compound, but in addition dimethyl *trans-cyclo*heptane-1 : 2-dicarboxylate (IX) was obtained. Mild alkaline hydrolysis of the latter gave the free acid (V), identical with the acid obtained previously from *cyclo*heptanone.

The Raney nickel used in the desulphurisation was rich in hydrogen [15] and isolation of a sulphur-containing product in these circumstances is unusual. Owen and Peto obtained a sulphide by a desulphurisation [16] and considered that this was due to its insolubility in the medium but this explanation cannot apply in the present case as the product was wholly soluble. The molecular formula and general characteristics of the compound point to a thiolactone structure of type (VIII), and this was confirmed when the compound was converted into *trans-cyclo*heptane-1 : 2-dicarboxylic acid (V) by alkaline hydrolysis followed by treatment with Raney nickel.




The *trans*-acid (V) was converted into *trans-bicyclo*[5 : 3 : 0]decan-9-one (XV) by the following route: Reduction of the dimethyl or the diethyl ester with lithium aluminium hydride gave *trans*-1 : 2-di(hydroxymethyl)*cyclo*heptane (XI). Direct reduction of the acid, even under forcing conditions, furnished *trans*-2-hydroxymethyl*cyclo*heptane-1-carboxylic acid (XII) as the predominant product. The ditoluene-*p*-sulphonate of the

[11] Bergmann and Pinchas, *Rec. Trav. chim.*, 1952, **71**, 161.
[12] Newman and Lloyd, *J. Org. Chem.*, 1952, **17**, 577.
[13] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[14] Wolfrom and Karabinos, *ibid.*, 1944, **66**, 909.
[15] Hauptmann and Wladislaw, *ibid.*, 1950, **72**, 707, 710.
[16] Owen and Peto, *J.*, 1955, 2383.

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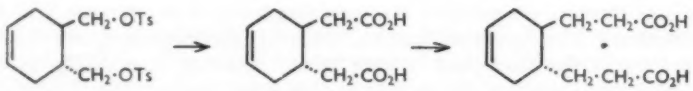
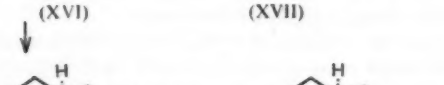
diol (XI) was readily obtained by Owen and Smith's method,[17] but did not yield the dinitrile (XIII) on reaction with potassium cyanide. Treatment of the diol (XI) with gaseous hydrogen bromide and of the resulting dibromide with aqueous-alcoholic potassium cyanide furnished the required dinitrile (XIII). Thorpe cyclisation of the dinitrile was effected by sodium in ethylene glycol, and the resulting imino-nitrile (XIV) was hydrolysed




(XVI) (XVII) (XVIII)




(XIX) (XX)

and decarboxylated by sulphuric–acetic acid. The semicarbazone and 2 : 4-dinitrophenylhydrazone of the ketone (XV) thus obtained were identical with those of the ketone obtained by the lithium–ammonia reduction of *bicyclo*[5 : 3 : 0]dec-7-en-9-one;[1] this saturated ketone must therefore be the *trans*-isomer. As this method of reduction usually gives the thermodynamically more stable isomer[18] this result seems to indicate that in simple systems the *trans*-fusion of a seven-membered and a five-membered ring is the more stable arrangement.

So far neither the *cis-cyclo*heptane-1 : 2-dicarboxylic acid nor any derivative of it has been obtained in this work. Hot acetic anhydride converted the *trans*-acid into the crystalline *trans*-anhydride, which was transformed back into the parent acid by mild aqueous hydrolysis. The *trans*-configuration of the anhydride was confirmed by reduction to the crystalline *trans*-diol (XI) by lithium aluminium hydride. Pyrolysis of the *trans*-acid at 240° furnished a liquid anhydride which differed significantly in infrared absorption characteristics from the solid anhydride. Reduction gave a non-crystalline diol whose ditoluene-*p*-sulphonate melted over a 10° range. Thus pyrolysis gave a mixture of anhydrides in which the *trans*-isomer probably predominated.

Another route to the *trans-bicyclo*decanone (XV) was explored but not completed. Reduction of diethyl *trans-cyclo*hex-4-ene-1 : 2-carboxylate by lithium aluminium hydride gave the corresponding *trans*-diol which was converted into the crystalline ditoluene-*p*-sulphonate (XVI). This derivative was treated with potassium cyanide, and the resulting dinitrile was hydrolysed to the *trans*-diacetic acid (XVII). A double Arndt–Eistert homologation furnished the crystalline *trans*-dipropionic acid (XVIII). An attempt to prepare this acid from the ditoluene-*p*-sulphonate (XVI) and diethyl sodiomalonate was unsuccessful, the sole product being the reduced *trans*-indane diester (XIX), readily converted into the crystalline monocarboxylic acid (XX) by hydrolysis and decarboxylation.

## Experimental

1-*Ethynyl*cyclo*heptanol*.—This was prepared from *cyclo*heptanone (191 g.) by the method of Heilbron *et al.*,[3] yielding 1-ethynyl*cyclo*heptan-1-ol (216 g., 91%), b. p. 97—100°/20 mm., $n_D^{25}$ 1·4868. A sample, crystallised from pentane, had m. p. 24·5—26°.

1-*Acetyl*cyclo*heptene*.—1-Ethynyl*cyclo*heptanol (216 g.), on treatment with Dowex 50 resin (14 g.) in glacial acetic acid (220 ml.),[4] gave 1-acetyl*cyclo*heptene (189·5 g., 88%), b. p. 99—102°/20 mm., $n_D^{25}$ 1·4924.

[17] Owen and Smith, *J.*, 1952, 4029.
[18] Barton and Robinson, *J.*, 1954, 3045.

*Reaction of* 1-*Acetyl*cyclo*heptene with Hydrogen Cyanide.*—The ketone (3·5 g., 0·025 mole) in alcohol (16 ml.) was added to a solution of potassium cyanide (3·25 g., 0·05 mole) in water (7·5 ml.). The solution was seeded with crystals of m. p. 131—135° obtained in a small-scale experiment and left at room temperature for 24 hr. The crystalline *product* (I) (2·05 g.) was obtained as needles, m. p. 150·5—152°, from aqueous alcohol (Found: C, 69·1; H, 8·0; N, 14·7. $C_{11}H_{16}ON_2$ requires C, 68·7; H, 8·4; N, 14·6%), $\nu_{max.}$ (in $CCl_4$) 3400, 3175 (bonded NH or OH), 1710, 1735 cm.$^{-1}$ (C=N?).

This product (0·75 g., 0·0039 mole) was refluxed with 2N-sodium hydroxide (6 ml.) for 5 hr., evolution of ammonia having by then ceased. The cooled solution was acidified with sulphuric acid, and the separated oil extracted into ether (2 × 10 ml.). Evaporation of the dry ethereal solution ($MgSO_4$) gave a thick oil (0·43 g., 67%) which crystallised on trituration with light petroleum (b. p. 40—60°). Recrystallisation from light petroleum–benzene gave 2-*acetyl*-cyclo*heptanecarboxylic acid*, m. p. 67—68·5° (Found: C, 65·1; H, 8·9. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·75%), $\nu_{max.}$ (dil. soln. in $CCl_4$) 3570 (free OH), 3350 (associated OH), 1780 (γ-lactone), 1705 cm.$^{-1}$ (ketone C=O).

*Large-scale Preparation of* 2-*Acetyl*cyclo*heptanecarboxylic Acid.*—1-Acetyl*cyclo*heptene (103·8 g., 0·75 mole) was added to a solution of potassium cyanide (107·5 g.) in water (200 ml.), and this was diluted with ethylene glycol (750 ml.). The mixture was not homogeneous but gave a clear solution after being stirred at room temperature for an hour. After a further hour's stirring potassium hydroxide (70 g.) in water (100 ml.) was added and the solution refluxed for 6 hr. The cool solution was extracted with ether (3 × 200 ml.), and the combined extracts were washed with water (50 ml.). Evaporation of the dry ethereal solution, and trituration in light petroleum (b. p. 40—60°), gave a neutral product (16·7 g.), m. p. 50—55°. As this material contained nitrogen and gave a high yield of the acid on further treatment with alkaline glycol it was probably a mixture of the intermediate 1-acetyl-2-cyano*cyclo*heptane and the corresponding amide.

The alkaline liquor was acidified with concentrated hydrochloric acid (270 ml.), and extracted with ether (4 × 200 ml.). The combined extracts were washed with water (30 ml.), dried ($MgSO_4$), and evaporated. The product (102·7 g., 74%) crystallised on being seeded with 2-acetyl*cyclo*heptanecarboxylic acid.

In another experiment acetyl*cyclo*heptene (23·0 g.) was converted into 2-acetyl*cyclo*heptane-carboxylic acid (29·4 g., 96%), by increasing the time of reflux to 22 hr.

*Esterification of* 2-*Acetyl*cyclo*heptane*-1-*carboxylic Acid.*—(*a*) The acid (4·5 g., 0·024 mole) was refluxed for 15 hr. in ethylene dichloride (13·0 ml.)–methanol (4·0 ml.) containing toluene-*p*-sulphonic acid (80 mg.). The solution was evaporated and the residue dissolved in ether (20 ml.), washed with 10% sodium carbonate solution (2 × 12 ml.) and water (5 ml.), and dried ($MgSO_4$). Distillation gave a mixture of the *pseudo*- (V) and normal ester (1·98 g., 51% after allowance for 0·86 g. of recovered acid), b. p. 80°/0·4 mm., $n_D^{25}$ 1·4702 (Found: C, 66·7; H, 9·25. Calc. for $C_{11}H_{18}O_3$: C, 66·6; H, 9·15%), $\nu_{max.}$ (liquid film) 1773 (γ-lactone), 1727, 1712 cm.$^{-1}$ (keto-ester).

(*b*) The acid (2·9 g., 0·016 mole), treated with diazomethane in ether in the usual way, gave the normal ester (2·08 g., 67%), b. p. 77°/0·3 mm., $n_D^{25}$ 1·4660, $\nu_{max.}$ (liquid film) 1726, 1712 cm.$^{-1}$ (keto-ester).

With Brady's reagent the normal ester gave an orange 2 : 4-*dinitrophenylhydrazone* in 95% yield. After chromatography on alumina (eluant, benzene containing 5% of ethyl acetate) the derivative crystallised from methanol, and had m. p. 100·5—102° (Found: C, 54·2; H, 5·8; N, 14·7. $C_{17}H_{22}O_6N_4$ requires C, 54·0; H, 5·9; N, 14·8%).

Under the same conditions the Clinton–Laskowski product gave the same 2 : 4-dinitrophenylhydrazone (mixed m. p.) in 72% yield.

The 2 : 4-dinitrophenylhydrazone of the parent 2-acetyl*cyclo*heptanecarboxylic acid (0·29 g.) was prepared by addition of a hot solution in methanol (2 ml.)–water (10 ml.) to 2 : 4-dinitrophenylhydrazine hydrochloride (0·5 g.) in hot water (15 ml.). The product was purified by chromatography on bentonite–kieselguhr (eluant, benzene containing 20% of chloroform). It was freely soluble in methanol and crystallised from carbon tetrachloride in orange needles, m. p. 183—184°. The sample retained solvent tenaciously, giving a positive reaction for chlorine in the Lassaigne test even after several hours' drying at 20°/3 × $10^{-3}$ mm. A loss of 10% occurred when the temperature was raised to 110° (Found: C, 52·1; H, 5·35; N, 14·6. Calc. for $C_{16}H_{20}O_6N_4$: C, 52·7; H, 5·5; N, 15·4%).

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trans-cyclo*Heptane*-1 : 2-*dicarboxylic Acid*.—2-Acetylcycloheptanecarboxylic acid (32·0 g., 0·18 mole) was stirred with sodium hypochlorite solution [9] (490 ml.; 10—14% of available chlorine); emulsification and refluxing of chloroform were noted after 45 min. After a further 5 hours' stirring the mixture had regained room temperature and excess of hypochlorite was reduced by the addition of sodium pyrosulphite (18 g.) in water. The product was acidified by sulphuric acid (30 g.) in water (50 ml.), and the oil obtained was separated by ether (100 ml.) and combined with the ether-extract (4 × 200 ml.) of the aqueous liquor. Evaporation of the dried ($MgSO_4$) extract gave the *dicarboxylic acid* as a white solid (30·5 g., 95%). After one crystallisation from benzene–light petroleum it had m. p. 142—146°. The analytical sample had m. p. 145—147° (Found: C, 58·0; H, 7·6. $C_9H_{14}O_4$ requires C, 58·0; H, 7·6%).

*Resolution of the Acid as the Brucine Salts.*—*trans-cyclo*Heptane-1 : 2-dicarboxylic acid (1·97 g., 0·011 mole; m. p. 142—146°) and anhydrous brucine (8·3 g.; m. p. 167—171°) were dissolved in hot ethyl acetate (30 ml.). The brucine salt began to separate from the warm solution almost immediately; it was filtered off after 48 hours. The white solid product (8·25 g., 80% of total) was extracted with boiling ethyl acetate (30 ml.) for 45 min. and the mixture filtered. In 24 hr. the filtrate deposited a crystalline product (*salt A*; 3·8 g., 37%), m. p. 129—132°, $\alpha$ −0·44°, $[\alpha]_D^{19}$ −15·2° ± 0·7° (*c* 2·9 in EtOH) unchanged in rotation by further crystallisation (Found: C, 62·6; H, 6·7; N, 5·7. $C_{55}H_{66}O_{12}N_4,4H_2O$ requires C, 63·0; H, 7·1; N, 5·35%).

Evaporation of the original ethyl acetate liquor gave a thick oil (*salt B*; 1·1 g.) which solidified when rubbed in ether, and then had $\alpha$ −0·68°, $[\alpha]_D^{20}$ −39·5° ± 0·7° (*c* 1·7 in EtOH). Evaporation of the liquor from the first crystallisation of salt A gave more of salt B (3·7 g.), $\alpha$ −0·38°, $[\alpha]_D^{20}$ −38° ± 1·0° (*c* 2·0 in EtOH, *l* 0·5 dm.). This did not crystallise; purified by precipitation from alcohol by ether, it had m. p. 101—108°, $[\alpha]_D^{19}$ −46·0° ± 1·0° (Found: C, 62·6; H, 6·9; N, 5·5%). The salts probably became hydrated on exposure to the atmosphere. There was no weight loss at 76°/0·05 mm., and a loss of only 1% after 3 hr. at 110°/$10^{-3}$ mm.

The brucine salts A and B (3·8 g.), $[\alpha]_D^{19}$ −15·2° and $[\alpha]_D^{20}$ −39·5°, were separately decomposed by stirring them with 2N-hydrochloric acid (25 ml.) for 4 min. at 0°. The acid solution was ether-extracted (3 × 20 ml.), and the combined extracts were washed with water (2 × 5 ml.), dried ($MgSO_4$), and evaporated below room temperature. Salt A gave an acid, m. p. 138—142°, $\alpha$ +0·41°, $[\alpha]_D^{19}$ +3·4° (±0·3°) (*c* 12·5 in EtOH). After one crystallisation from benzene this had m. p. 142—145°, $[\alpha]_D^{19}$ +1·6° (±0·4°). Partial racemisation also occurred during crystallisation from benzene–light petroleum (b. p. 60—80°). Salt B gave an acid, m. p. 138—141°, $\alpha$ −0·19°, $[\alpha]_D^{18}$ −4·7° (±0·5°) (*c* 8·2 in EtOH, *l* 0·5 dm.). The rotation of this sample was unchanged when the ethanolic solution was kept overnight at room temperature, but after crystallisation from benzene the material had $[\alpha]_D^{19}$ −1·0° (±0·2°). The time interval between the commencement of the acid treatment and the first reading of the polarimeter was 50 min. for the (+)-acid and 56 min. for the (−)-acid.

*Dimethyl* trans-cyclo*Heptane*-1 : 2-*dicarboxylate*.—The dicarboxylic acid (1·18 g., 0·006 mole) was treated with diazomethane in ether and worked up after being kept overnight. The *product* (1·10 g., 81%) boiled at 74—81°/0·5 mm.; redistillation gave pure material, b. p. 78°/0·5 mm., $n_D^{25}$ 1·4602 (Found: C, 61·85; H, 8·5. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·5%).

*Diethyl* trans-cyclo*Heptane*-1 : 2-*dicarboxylate*.—The dicarboxylic acid (5·7 g., 0·03 mole) was converted by Cope and Herrick's method [10] into the *diethyl ester* (6·6 g., 89%), b. p. 80°/0·2 mm., $n_D^{25}$ 1·4556 (Found: C, 64·6; H, 8·9. $C_{13}H_{22}O_4$ requires C, 64·4; H, 9·15%).

*Attempted Inversion of Diethyl* trans-cyclo*Heptane*-1 : 2-*dicarboxylate*.—The diethyl ester (6·25 g., 0·026 mole) was refluxed in ethanol (20 ml.) containing sodium (1·0 g.) for 3 hr.; after 16 hr. water (10 ml.) was added and the solution evaporated under reduced pressure. The residue (4·6 g.) was taken up in 2N-sodium hydroxide (30 ml.), extracted with ether (2 × 15 ml.), acidified with sulphuric acid, and again ether-extracted (3 × 20 ml.). The last extracts were dried and evaporated, to give an acid (3·0 g.) which crystallised under light petroleum. Crystallisation from benzene raised the m. p. to 145—147·5°, not depressed on admixture with the starting acid.

*Reactions of the Diethyl Ester with Bases*.—There was no apparent reaction between the ester and ammonia solution (*d* 0·88) during several days' shaking at room temperature.

The ester (0·72 g., 0·003 mole) dissolved in 100% hydrazine hydrate (3 ml.) during 1·5 hours'

[10] Cope and Herrick, *Org. Synth.*, 1950, **30**, 29.

refluxing; the cooled solution deposited the *dihydrazide* as needles, m. p. 150—155°. Desiccation over sulphuric acid gave crude material (0·65 g., 100%); pure material had m. p. 156—157° (from *tert.*-butyl alcohol) (Found: C, 50·6; H, 8·4; N, 25·9. $C_9H_{18}O_2N_4$ requires C, 50·45; H, 8·5; N, 26·15%).

trans-cyclo*Heptane*-1 : 2-*dicarboxylic Anhydride*.—The *trans*-acid (800 mg.) was refluxed in acetic anhydride for 2 hr. Excess of acetic anhydride was removed under a vacuum and the residue distilled, to give the *anhydride* (557 mg., 77%), b. p. 94°/0·25 mm., $n_D^{25}$ 1·4920, which solidified and, crystallised from hexane–ether, had m. p. 43—45° (Found: C, 63·2; H, 7·1. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%. The carbon analyses were consistently low), $\nu_{max.}$ (in $CCl_4$) 1785, 1870 cm.$^{-1}$ (C=O of 5-ring anhydride).

The anhydride (45 mg.) dissolved in boiling water (0·3 ml.) in 2 min., and the cooled solution deposited crystals of the *trans*-dicarboxylic acid (33 mg.), m. p. and mixed m. p. 145—146·5°.

Reduction of this anhydride (557 mg.) by lithium aluminium hydride (600 mg.) in refluxing ether for 3 hr. gave the *trans*-glycol (491 mg., 94%), m. p. 55—57° undepressed by authentic material (see below).

*Mixed Anhydrides of* cyclo*Heptane*-1 : 2-*dicarboxylic Acid*.—The *trans*-acid (400 mg.) was added in small amounts to a small flask maintained at 240° (bath). Addition was complete in 5 min. and after a further 5 minutes' heating the residual anhydride was distilled (b. p. 98°/0·2 mm.; $n_D^{23}$ 1·4928; 258 mg., 71%) but did not crystallise (Found: C, 64·5; H, 6·7. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·2%): it had infrared max. in $CCl_4$ at 1783 and 1868 cm.$^{-1}$ (C=O of 5-ring anhydride).

Reduction (of 258 mg.) by lithium aluminium hydride was carried out as for the pure *trans*-anhydride; the glycol obtained (227 mg., 93%) did not crystallise, but gave a ditoluene-*p*-sulphonate, m. p. 75—83° (from methanol), under conditions described below. A mixture with the authentic *trans*-ditoluene-*p*-sulphonate (m. p. 89—90°; see below) had m. p. 80—90°.

trans-1 : 2-*Di*(*hydroxymethyl*)cyclo*heptane*.—(*a*) *trans-cyclo*Heptane-1 : 2-dicarboxylic acid (0·80 g., 0·004 mole) in ether (10 ml.) was added to lithium aluminium hydride (0·40 g., 66% excess) in ether (15 ml.) during 15 min. with ice-cooling. The mixture was stirred at room temperature for 2 hr. and the excess of hydride then destroyed with ethyl acetate. After acidification with sulphuric acid (4 g. in 10 ml. of water) the ether layer was separated and extracted with water (3 × 10 ml.). Continuous ether-extraction of the combined aqueous liquors yielded a residue (0·15 g., 22%) which crystallised under light petroleum (b. p. 40—60°). This material was the required *diol* which crystallised from hexane–ether in prisms, m. p. 56—57° (Found: C, 68·6; H, 11·2. $C_9H_{18}O_2$ requires C, 68·3; H, 11·5%).

Evaporation of the original ether layer yielded a residue of trans-2-*hydroxymethyl*cyclo*heptanecarboxylic acid* (0·48 g., 65%) which solidified under light petroleum (b. p. 40—60°) to a crystalline mass, m. p. 64—70°, raised to 77—79° on crystallisation from benzene–light petroleum (b. p. 40—60°) [Found: C, 62·9; H, 9·6. $C_9H_{16}O_3$ requires C, 62·8; H, 9·4%) and had $\nu_{max.}$ in $CHCl_3$ at 2400—3640 (chelated OH) and 1710 cm.$^{-1}$ (C=O of acid). Under more forcing conditions, *i.e.*, 4 hours' refluxing with a five-fold excess of lithium aluminium hydride, the dicarboxylic acid (1·02 g.) was converted into a mixture of the same two products, diol (0·35 g., 40%) and hydroxy-acid (0·45 g., 48%).

(*b*) Diethyl *trans*-1 : 2-*cyclo*heptanedicarboxylate (13·6 g., 0·056 mole) was refluxed for 2 hr. with lithium aluminium hydride (5·5 g., 80% excess) in ether. The mixture was worked up as usual and gave only the diol (8·1 g., 90%), m. p. 53—56°.

*Ditoluene-p-sulphonate of* trans-1 : 2-*Di*(*hydroxymethyl*)cyclo*heptane*.—This was prepared from the diol (1·80 g., 0·0011 mole) by Owen and Smith's method [17] and worked up after 45 hr. at 0°, to yield a crude *ester*, m. p. 80—85° (3·94 g., 74%), which crystallised from methanol as needles, m. p. 89—90° (Found: C, 59·3; H, 6·5. $C_{23}H_{30}O_6S_2$ requires C, 59·2; H, 6·45%).

*Reaction with potassium cyanide*. The ditoluene-*p*-sulphonate (2·93 g.) was refluxed for 1 hr. in ethylene glycol (18 ml.) containing potassium cyanide (1·25 g. in 2 ml. of water). The cooled liquor was extracted with ether (4 × 15 ml.), and the dried extract was evaporated to a clear oil (0·91 g.). The bulk of this material was undistillable but a small fraction (0·18 g.) of b. p. 44°/0·7 mm. was obtained. This material was soluble in light petroleum (b. p. 40—60°), contained neither nitrogen nor sulphur, and rapidly decolorised bromine in carbon tetrachloride.

trans-1 : 2-*Di*(*bromomethyl*)cyclo*heptane*.—A stream of dry hydrogen bromide was passed into *trans*-1 : 2-di(hydroxymethyl)*cyclo*heptane (3·55 g., 0·022 mole) at 110° (bath). Uptake of hydrogen bromide had almost ceased after 15 min., but passage of the gas was continued for

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a further 15 min. at 110°. The cooled residue was stirred with 10% potassium carbonate solution (20 ml.), the insoluble oil taken up in light petroleum (20 ml., b. p. 60—80°), and this solution dried over potassium carbonate. Distillation yielded the *dibromo-compound* (3·1 g., 53%), b. p. 84°/0·3 mm., $n_D^{27}$ 1·5378 (Found: C, 38·1; H, 5·85; Br, 56·3. $C_9H_{16}Br_2$ requires C, 38·0; H, 5·7; Br, 56·3%).

*Reaction with potassium cyanide.* The dibromo-compound (3·0 g., 0·01 mole) was gently refluxed in ethylene glycol (18 ml.) containing potassium cyanide (2·6 g.) for 10 min. The cooled product (discoloured) was extracted with ether (3 × 15 ml.), and the ether layer washed with water (4 ml.). Evaporation of the dried extract gave an oil (1·56 g.) which was bromine-free; this was distilled, giving the *dinitrile* (1·07 g., 57%), b. p. mainly 106°/0·1 mm. Redistilled material had b. p. 112°/0·6 mm., $n_D^{21}$ 1·4950 (Found: C, 75·2; H, 9·0; N, 15·4. $C_{11}H_{16}N_2$ requires C, 74·95; H, 9·15; N, 15·9%), $\nu_{max.}$ (liquid film) 2258 cm.$^{-1}$ (C≡N).

When the time of refluxing in glycol was increased to 30 min. the material obtained by ether-extraction was partly crystalline. Needles, m. p. 152—158°, were separated from the dinitrile by crystallisation from aqueous methanol and represented 31% of the total yield. Crystallisation from methanol gave pure material, m. p. 160·5—162°, identical with the product from Thorpe cyclisation of the dinitrile (see below).

The dibromo-compound (2·9 g., 0·01 mole) was also treated with potassium cyanide (2·6 g.) in ethanol (25 ml. containing 4 ml. of water) and refluxed for 1·5 hr., the yield of dinitrile being 62%.

*Thorpe Cyclisation of* trans-1 : 2-*Di*(*cyanomethyl*)cyclo*heptane*.—(*a*) The dinitrile (231 mg.) was refluxed in absolute alcohol (1 ml.) containing sodium (10 mg.) for 1 hr. Dilution with water (3 ml.) led to the separation of an oil which did not crystallise on being seeded and was presumed to be starting material. (*b*) The nitrile (973 mg.) was refluxed in ethylene glycol (5 ml.) containing sodium (120 mg.) for 45 min.; dilution with water (8 ml.) precipitated crystals (730 mg., 75%), m. p. 153—157°. The pure trans-8-*cyano*-9-*imino*bicyclo[5 : 3 : 0]*decane* (XIV) had m. p. 161—162° (methanol) (Found: C, 75·1; H, 8·7; N, 15·9. $C_{11}H_{16}N_2$ requires C, 74·95; H, 9·15; N, 15·9%), $\nu_{max.}$ (in $CHCl_3$) 3487, 3387 (NH), 2187 (C≡N), 1644, 1610 cm.$^{-1}$ (C=N). Unchanged nitrile (98 mg., 10% recovery) was obtained by ether-extraction of the liquor. Cyclisation did not take place when the concentration of sodium glycoside was one-third of that shown above.

trans-bicyclo[5 : 3 : 0]*Decan*-9-*one*.—(*a*) The imino-nitrile (XVI) (215 mg.) from the Thorpe cyclisation was hydrolysed, with decarboxylation, by Ziegler's method.[20] After 3·5 hours' refluxing, steam-distillation and ether-extraction of the distillate yielded *trans-bicyclo*[5 : 3 : 0]-decan-9-one (24 mg. 13%). (*b*) The imino-nitrile (73 mg.) was treated as above, but with continuous steam-distillation. A good yield (45·5 mg.) of material was isolated from the distillate, but reaction was incomplete, since the product contained nitrogen and gave only a small quantity of semicarbazone on being treated with semicarbazide acetate in methanol. (*c*) The imino-nitrile (116 mg.) was treated as in (*a*) but in a solution made homogeneous by the addition of glacial acetic acid. Steam-distillation and ether-extraction of the distillate (dried with sodium carbonate) yielded the ketone (52 mg., 51%).

The ketone gave a high yield of the semicarbazone, m. p. 214—216·5° (Islam and Raphael [1] give 221—223°), which with 2 : 4-dinitrophenylhydrazine sulphate yielded an orange 2 : 4-dinitrophenylhydrazone, m. p. 136—138°, undepressed by the material obtained by Islam and Raphael (m. p. 138°).

*Dimethyl* trans-1 : 2-4-*Oxo*cyclo*hexanedicarboxylate*.—Fumaroyl chloride (4·75 g., 0·03 mole) in dry ether (10 ml.) was added with stirring and ice cooling, during 20 min., to 2-ethoxybuta-1 : 3-diene [21] (3·5 g., 0·036 mole) in ether (10 ml.). The yellow solution was stirred for a further 2·5 hr. at room temperature and was then added, with stirring, to dry methanol (40 ml.). Stirring was continued for 1 hr. and the solution neutralised by the gradual addition of solid sodium hydrogen carbonate. The mixture was filtered, dried ($MgSO_4$), and evaporated, and the oil obtained was distilled; it had b. p. 110—114°/0·6 mm., $n_D^{27}$ 1·4724 (3·70 g., 56%). The *keto-diester* crystallised: from ether–light petroleum (b. p. 40—60°), had m. p. 53—54° (Found: C, 56·0; H, 6·6. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·6%), $\nu_{max.}$ (in $CCl_4$) 1748 cm.$^{-1}$ (combined ester and ketone C=O). The *semicarbazone*, obtained with semicarbazide acetate in boiling

[20] Ziegler in "Methoden der Organischen Chemie," Georg Thieme, Stuttgart, 1955, Vol. IV, Part 2, p. 758.

[21] Braude, Jones, Sondheimer, and Toogood, *J.*, 1949, 613.

methanol, had m. p. 171—172° (from methanol) (Found: C, 48·5; H, 6·25; N, 15·3. $C_{11}H_{17}O_5N_3$ requires C, 48·7; H, 6·3; N, 15·5%).

When this experiment was repeated (scale, 0·1 mole) and the product neutralised by *rapid* addition of solid sodium hydrogen carbonate, a mixture was obtained. One component, the *dimethyl ketal* (6·0 g.) of the keto-ester separated as prisms, m. p. 60—65°, on being stirred in ether and a further quantity (12·5 g., overall yield 70%) was obtained by evaporating the liquor and stirring the residue in light petroleum (b. p. 40—60°). Recrystallisation from benzene–light petroleum (b. p. 40—60°) raised the m. p. to 75·5—76·5° (Found: C, 55·3; H, 7·4. $C_{12}H_{20}O_6$ requires C, 55·4; H, 7·75%). Infrared absorption was at 1742 (ester C=O), 1169, 1127, 1096 cm.$^{-1}$ (C·O·C of ketal). Evaporation of the petroleum washings yielded the second component (3·85 g., 17%), the keto-diester described above.

The ketal (13·3 g., 0·05 mole) was shaken for 1 hr. in 2N-hydrochloric acid (40 ml.), whence ether-extraction yielded the keto-diester (9·9 g., 89%), m. p. 39—45°, undepressed by pure material.

trans-4-*Oxo*cyclo*hexane*-1 : 2-*dicarboxylic Acid.*—The dimethyl ester (3·20 g., 0·015 mole) was refluxed with potassium hydroxide (3·0 g.) in water (12 ml.) for 1 hr., and the cooled solution was acidified with concentrated hydrochloric acid (4 ml.) and evaporated to dryness under reduced pressure. The residue (9·2 g.) was extracted with dry acetone in a Soxhlet extractor; extraction was complete in 1·5 hr. Evaporation of the acetone gave a residue, m. p. 162—168° (2·80 g., 100%), raised to 186—188° by crystallisation from acetic acid (Found: C, 51·7; H, 5·3. $C_8H_{10}O_5$ requires C, 51·6; H, 5·4%). The pure *acid* was almost insoluble in acetone and in subsequent extractions, in the presence of seed crystals, it was necessary to use dioxan as solvent.

Standard ethereal diazomethane (23 ml. containing 2 equivs.) was added dropwise to a stirred suspension of the acid (0·49 g., 0·0026 mole) in ether (8 ml.). Rapid evolution of nitrogen occurred and a clear solution was obtained in 15 min. This ethereal solution (diluted to 50 ml.) was washed with saturated sodium hydrogen carbonate solution (5 ml.), dried ($MgSO_4$), and evaporated. The semisolid residue was distilled (b. p. 100—103°/0·35 mm.; 0·47 g., 82%) and when stirred in light petroleum (b. p. 40—60°) gave crystals of dimethyl *trans*-4-oxo*cyclo*hexane-1 : 2-dicarboxylate, m. p. 46—49° undepressed on admixture with material obtained in the Diels–Alder reaction.

*Dimethyl* trans-*Oxo*cyclo*heptane*-1 : 2-*dicarboxylate.*—The preceding ester (4·95 g., 0·023 mole) was diluted with methanol (5 ml.); a little sodium carbonate (0·4 g.) was added and the solution stirred in a bath at 60°. After addition of a small portion of methylnitrosourethane there was an induction period of about 15 min. As soon as evolution of nitrogen began, the remainder of the urethane (2·60 g. in all, 0·020 mole; b. p. 32—34°/1 mm.) was added as quickly as possible and the reaction proceeded rapidly. The crude product contained up to 15% of starting material, which was removed by selective reaction with semicarbazide acetate in methanol. After filtration from the semicarbazone the solution was evaporated, the residue stirred with ether, and the ether-soluble material was distilled (b. p. 94—96°/3 × $10^{-3}$ mm., $n_D^{23}$ 1·4718). The product (3·19 g., 72%) crystallised; recrystallised from pentane, it had m. p. 60—64° but satisfactory analyses could not be obtained (Found: C, 58·9; H, 7·6. Calc. for $C_{11}H_{16}O_5$: C, 57·9; H, 7·1%). Infrared absorption (in $CCl_4$) occurred at 1742 cm.$^{-1}$ (combined ester and ketone C=O).

*Reactions of Dimethyl* trans-*Oxo*cyclo*heptane*-1 : 2-*dicarboxylate with Thiols, followed by Raney Nickel.*—(*a*) The keto-ester (2·40 g., 0·011 mole) in dry ether (2 ml.) was added to ethanethiol (1·34 g., 10% excess) in ether (4 ml.), containing freshly fused zinc chloride (2·0 g.) and sodium sulphate (2·0 g.). The mixture was cooled in ice during the 10 min required for the addition, and was shaken at room temperature for a further 1·5 hr. before being poured on ice-water–ether (5 ml. of ether). The ether layer was separated and the aqueous layer extracted with ether (10 ml.). The combined ether layers were washed with 5% sodium hydroxide solution (5 ml.), dried ($MgSO_4$), and evaporated, to give a sulphur-containing residue (2·20 g.) which did not crystallise.

The oil from the thiol condensation was dissolved in ethanol (25 ml.) and refluxed with Raney nickel (8 g.) for 40 min.; evolution of gas had then ceased. The mixture was filtered, the filtrate evaporated, and the product freed from a trace of inorganic material by dissolution in ether and filtration. Evaporation of ether gave a residue (1·09 g.) which was distilled, to give a sulphur-containing product, b. p. 110—114°/0·5 mm. [0·78 g. corresponding to a yield

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of 35% of (VIII)]. Analytical *thiolactone* (VIII) had b. p. 111°/0·35 mm., $n_D^{25}$ 1·4872 (Found: C, 56·2; H, 6·7; S, 14·85. $C_{10}H_{14}O_3S$ requires C, 56·1; H, 6·6; S, 14·9%), $\nu_{max.}$ (in $CCl_4$) 1738 (C=O), 1445, 1330, 1275, 1205, 1175, 1020 cm.$^{-1}$.

(*b*) The keto-ester (2·40 g.) was condensed with ethanedithiol (1·5 g.) under the conditions described above, and the product worked up in the same way except that organic material was extracted into benzene, not ether. Evaporation of benzene gave a sulphur-containing oil (2·67 g.) which was treated with Raney nickel (8 g.) in ethanol (25 ml.) as above. The oil (1·37 g.) obtained was distilled, giving fractions (i) b. p. 84—87°/0·8 mm. (0·34 g.), $n_D^{25}$ 1·4611 and (ii) b. p. 124—128°/1·0 mm. (0·84 g.), $n_D^{25}$ 1·4820. A portion of fraction (i) (66 mg.) was hydrolysed in boiling 15% sodium hydroxide solution and yielded *trans-cyclo*heptane-1 : 2-dicarboxylic acid (44 mg., 78%), m. p. 141—144° (benzene), undepressed on admixture with the acid obtained as above (m. p. 145—147°). A portion (111 mg.) was reduced with lithium aluminium hydride in ether to the *trans*-diol (43 mg., 60%), a thick oil which was converted into the ditoluene-*p*-sulphonate, m. p. and mixed m. p. 89—90°. Fraction (ii) was redistilled and identified as thiolactone (VIII) by its infrared spectrum.

*Reactions of the Thiolactone* (VIII).—The thiolactone (VIII) (207 mg.) was refluxed in 15% sodium hydroxide solution (12 ml.) for 2 hr. and the cooled product extracted with ether (10 ml.) to remove a little insoluble material. The aqueous layer was acidified with concentrated hydrochloric acid (5 ml.) and extracted with ether (3 × 10 ml.). Evaporation of the dried ($MgSO_4$) extract gave a thick oil (132 mg.) containing sulphur. This was refluxed in ethanol (8 ml.) containing Raney nickel (1 g.) for 1 hr. Filtration and evaporation of the filtrate yielded a pale green solid, insoluble in ether and having m. p. 220°. This was presumably a nickel salt; it was dissolved in 2N-hydrochloric acid (5 ml.) and extracted with ether (3 × 5 ml.). Evaporation of the dry extract gave an oil (50 mg.) which crystallised under light petroleum (b. p. 60—80°) to a solid with m. p. 127—135°. Recrystallisation from benzene–light petroleum (b. p. 60—80°) raised the m. p. to 144—146°, undepressed on admixture with authentic *trans-cyclo*heptane-1 : 2-dicarboxylic acid, m. p. 145—147° (overall yield from thiolactone, 28%).

*Diethyl* trans-cyclo*Hex*-4-*ene*-1 : 2-*dicarboxylate*.—The corresponding *cis*-ester was prepared in 89% yield by Cope and Herrick's method [19] and was inverted by sodium ethoxide in boiling ethanol, to give the *trans*-acid, m. p. 170—171°.[22] This acid was converted into the diethyl ester by Cope and Herrick's method.[19] The product (68% yield) had b. p. 74—78°/0·1 mm., $n_D^{25}$ 1·4673 (Petrov and Sopov [23] give b. p. 150·5—151·5°, $n_D^{20}$ 1·4592).

trans-4 : 5-*Di*(*hydroxymethyl*)cyclo*hexene*.—Diethyl *trans-cyclo*hex-4-ene-1 : 2-dicarboxylate (31·6 g., 0·14 mole) was reduced with lithium aluminium hydride (8·3 g., 50% excess) and, after being stirred overnight, was worked up as usual. The *diol* (15·3 g., 77%), m. p. 39—40° (from hexane–ether), had b. p. 101—102°/0·15 mm., $n_D^{25}$ 1·5048 (Found: C, 67·4; H, 9·5. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). The corresponding *cis*-diol [24, 25] has m. p. 34·5°.

The diol (15·3 g., 0·11 mole) was treated with toluene-*p*-sulphonyl chloride (41·3 g.) as described by Owen and Smith.[17] The mixture was worked up after 48 hr. at 0° to give the *ditoluene*-p-*sulphonate* (44·4 g., 92% yield) as plates, m. p. 94—95·5°, from methanol (Found: C, 58·7; H, 5·8. $C_{22}H_{26}O_6S_2$ requires C, 58·6; H, 5·8%). The *cis*-derivative [25] has m. p. 97·5°.

*Reaction between the Ditoluene*-p-*sulphonate and Diethyl Sodiomalonate*.—The sodio-derivative was prepared by the addition of a solution of sodium (1·06 g., 0·046 g.-atom) in dry ethanol (100 ml.) to diethyl malonate (32 g., 0·2 mole). Sodium iodide (2·0 g.) was dissolved in dry ethanol (35 ml.), half the solvent was distilled off in a dry atmosphere, and the residue added to the solution of diethyl sodiomalonate. The ditoluene-*p*-sulphonate (9·0 g., 0·02 mole) in benzene (50 ml.) was added during 2·75 hr. to the vigorously stirred solution, which was refluxed during the addition and for a further 18 hr. The cooled solution was filtered from insoluble sodium toluene-*p*-sulphonate and evaporated under reduced pressure. The sodio-derivative was decomposed by shaking the residue with benzene (80 ml.)–water (40 ml.), and the residue obtained on evaporation of the benzene layer was distilled, to give diethyl *trans-bicyclo*[4 : 3 : 0]non-3-ene-8 : 8-dicarboxylate (4·6 g., 87%), b. p. 90—92°/3 × $10^{-3}$ mm., $n_D^{25}$ 1·4718.

This diethyl ester was hydrolysed under reflux for 6 hr. in methanol (35 ml.) containing

[22] Alder *et al.*, *Annalen*, 1950, **570**, 244; 1949, **564**, 103.
[23] Petrov and Sopov, *Sbornik Statei po obshchei Khim.*, 1953, **2**, 853; *Chem. Abs.*, 1955, **49**, 5329.
[24] Eliel and Pillar, *J. Amer. Chem. Soc.*, 1955, **77**, 3600.
[25] Braude, personal communication.

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potassium hydroxide (15 g. in a little water). Methanol was removed in steam, and the aqueous solution remaining was extracted with ether (25 ml.); this extract was discarded and the aqueous solution acidified with 30% sulphuric acid; trans-bicyclo[4 : 3 : 0]*non-3-ene-8* : 8-*dicarboxylic acid* (2·92 g., 81%) separated, having m. p. 181—183°, raised to 184—186° by crystallisation from hot water (Found: C, 63·0; H, 6·6. $C_{11}H_{14}O_4$ requires C, 62·8; H, 6·7%).

trans-bicyclo[4 : 3 : 0]*Non-3-ene-8-carboxylic Acid.*—The dicarboxylic acid (2·25 g., 0·017 mole) was decarboxylated at 185—205°. The crystalline residue of *monocarboxylic acid* (1·75 g., 100%) sublimed at 90—110° (bath)/$10^{-4}$ mm., and then had m. p. 53—55° (Found: C, 72·4; H, 8·4. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%).

trans-4 : 5-*Di*(*cyanomethyl*)cyclo*hexene.*—The ditoluene-*p*-sulphonate (16·4 g., 0·033 mole) was dissolved in hot ethylene glycol (100 ml.) containing potassium cyanide (6·9 g., 1·5 equiv.) and water (8 ml.). Heating under reflux was continued for 2 hr. and the cooled alkaline solution extracted with ether (4 × 75 ml.). Evaporation of the dried extracts yielded the *dinitrile* (4·65 g., 59%) which crystallised from aqueous methanol in needles, m. p. 79·5—80·5° (Found: C, 74·8; H, 7·3. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·55%). Ether-extraction of the acidified liquors yielded the diacetic acid (1·4 g., 20%; see below). The *cis*-dinitrile [25] has m. p. 50°.

trans-cyclo*Hex-4-ene*-1 : 2-*diacetic Acid.*—The dinitrile (1·00 g., 0·006 mole) was refluxed with 33% potassium hydroxide solution (7 ml.) for 4 hr.; evolution of ammonia had then almost ceased. The cooled liquor was extracted with ether (8 ml.) and acidified with concentrated hydrochloric acid (3 ml.), and the precipitated *acid* (1·14 g., 92%) was filtered off as needles, m. p. 194—197°, raised to 199—200° by crystallisation from hot water (Found: C, 60·5; H, 7·0. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%). The *cis*-diacetic acid [25] has m. p. 157°.

trans-4 : 4-*Di*-(2-*carboxyethyl*)cyclo*hexene.*—The diacetic acid (1·00 g.; 0·005 mole) was added to excess of thionyl chloride (4 ml.), and the mixture refluxed for 10 min. Excess of thionyl chloride was removed under reduced pressure. The residue crystallised when stirred in ether and was added as a slurry in ether–benzene to diazomethane (from 3·3 g. of methylnitrosourea) in benzene. During the 30 min. taken for the addition the mixture was stirred at −10°, and afterwards for 1·5 hr. at room temperature. The mixture was kept for a further 36 hr. at 0° and the solvent was evaporated below 30°. The residue (1·05 g.) was dissolved in benzyl alcohol (5 ml.)–γ-collidine (5 ml.) and heated rapidly to 170° by immersion in a preheated oil bath; [26] rapid evolution of nitrogen occurred, which ceased after 8 min. The cooled residue was taken up in ether (40 ml.), filtered from insoluble material, washed with 2N-hydrochloric acid and water, dried, and evaporated, to give the crude dibenzyl ester (3·1 g.).

The ester was hydrolysed for 3·5 hr. in refluxing methanol (10 ml.) and 45% aqueous potassium hydroxide (10 ml.). The mixture was evaporated, and the residue taken up in water (15 ml.) and ether-extracted (2 × 20 ml.); the extracts were rejected. Acidifying the aqueous layer with concentrated hydrochloric acid (9 ml.) precipitated a solid which was extracted into ether (3 × 15 ml.). Drying and evaporation furnished a crystalline residue of the *dipropionic acid* (0·43 g., 43%), m. p. 166—172°. Analytical material crystallised from hot water in prisms, m. p. 172—172·5° (Found: C, 63·8; H, 7·85. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%).

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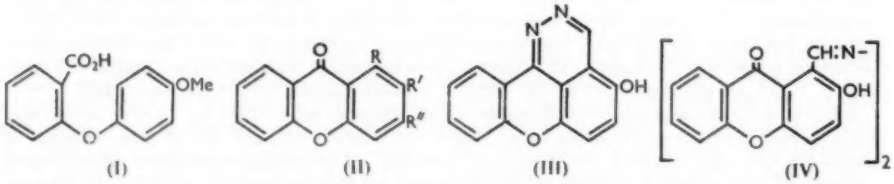
[26] Wilds and Meader, *J. Org. Chem.*, 1948, **13**, 763.

## 367. *Studies in the Xanthone Series. Part II.* Preparation and Reactions of 1-Formyl-2-hydroxyxanthone.*

By (the late) J. S. H. Davies, F. Lamb, and H. Suschitzky.

Reactions of 2-hydroxyxanthone leading to the preparation of 1-formyl-2-hydroxyxanthone (II; R = CHO, R′ = OH, R″ = H), furanoxanthones (V), and α-pyronoxanthones (VI) are discussed.

We have investigated reactions of 2-hydroxyxanthone in an attempt to find simple structural analogues of pharmacologically active chromones, such as khellin. We failed to obtain 2-hydroxyxanthone (II; R = R″ = H, R′ = OH) from salicylic acid and quinol,[1] but it was made by cyclisation of the diphenyl ether (I) (prepared from *o*-chlorobenzoic acid and *p*-methoxyphenol) with acetyl chloride–sulphuric acid or polyphosphoric acid, followed by demethylation.




(I) (II) (III) (IV)

*o*-Fluorobenzoic acid did not afford the ether (I), so it appears that fluorine prevents the carboxylate group from exerting its *ortho*-activating effect in the Ullmann copper-catalysed reactions of aryl halides with phenols. Recent observations that the *o*-carboxylate group is deactivating for methoxy-dechlorination [2,3] may be pertinent in this respect. Successful Ullmann reactions have been reported for *o*-fluorobenzoic esters.[4]

Attempts to cyclise 2-acetonyloxyxanthone (II; R = R″ = H, R′ = O·CH$_2$·COMe) with sulphuric acid or sulphuric acid–acetic acid were unsuccessful. Moreover, since neither bromoacetal nor ethyl β-bromopropionate condensed with 2-hydroxyxanthone, ring-closure of such ethers as a route to extended xanthone systems was abandoned.

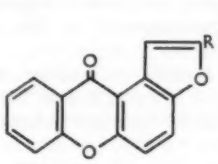
2-Hydroxyxanthone was readily formylated by a Duff reaction or, less conveniently, under Reimer–Tiemann conditions. The resulting aldehyde is 1-formyl-2-hydroxyxanthone (II; R = CHO, R′ = OH, R″ = H) for the following reasons: A Dakin reaction with the aldehyde yields a dihydroxyxanthone, convertible into a methylene ether. Moreover, the diacetyl and the dimethyl derivative differ from those of the alternative 2 : 3-dihydroxyxanthone (II; R′ = R″ = OH, R = H).[5,6] Treatment of the dihydroxy-compound with pyroboroacetate gives a monoacetyl derivative only, and one of the hydroxyl groups shows reduced reactivity (cf. Table: preparation of 2-substituted 1 : 2-dihydroxyxanthones). Both these results are explicable on grounds of chelation [7,8] and thus confirm the 1-position of the newly introduced hydroxyl group. That the two functional groups in the aldehyde are adjacent also follows from successful cyclisations of certain formylhydroxyxanthone derivatives (cf. below). Although the carbonyl reactivity

* Part I, *J.*, 1956, 2140.

[1] von Kostanecki and Rutishauser, *Ber.*, 1892, **25**, 1648.
[2] Miller and Williams, *J.*, 1953, 1475.
[3] Bunnett, Morath, and Okamoto, *J. Amer. Chem. Soc.*, 1955, **77**, 5055.
[4] Dean and Whalley, *J.*, 1954, 4638.
[5] Liebermann and Lindenbaum, *Ber.*, 1904, **37**, 2735.
[6] Cavill, Robertson, and Whalley, *J.*, 1949, 1567.
[7] Robertson and Waters, *J.*, 1929, 2239.
[8] King, King, and Manning, *J.*, 1953, 3932.

of xanthones is stated to be increased in reactions that can lead to ring formation,[9] reaction with hydrazine gave the aldazine (IV) and not the pyridazine (III).

Cyclisation of 1-formyl-9-oxo-2-xanthyloxyacetate (II; R = CHO, R′ = O·$CH_2$·$CO_2$Et, R″ = H) (prepared from 1-formyl-2-hydroxyxanthone and ethyl bromoacetate) in ethanol with sodium ethoxide at room temperature gave 5′-ethoxycarbonylfurano(3′ : 2′-1 : 2)-xanthone (V; R = $CO_2$Et) in good yield. Hydrolysis of this ester, followed by decarboxylation, yielded the parent furanoxanthone (V; R = H), which was also obtained in one step by ring-closure of the xanthyloxyacetic acid (II; R = CHO, R′ = O·$CH_2$·$CO_2$H, R″ = H) owing to accompanying decarboxylation.



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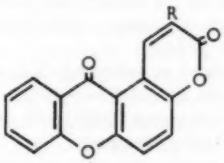

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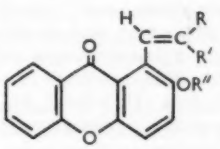

(VII)

1-Formyl-2-hydroxyxanthone readily underwent a Perkin reaction with acetic or propionic anhydride, yielding the α-pyronoxanthone (VI; R = H) or its homologue (VI; R = Me) respectively. Methylation of the pyrono-compounds in acetone with dimethyl sulphate, a modification [10] of the method used by Canter and Robertson [11] for identifying coumarin structures, afforded the unsaturated esters (VII; R = $CO_2$Me, R′ = H, R″ = Me; and R = $CO_2$Me, R′ = R″ = Me). By analogy with the behaviour of coumarin these esters and the acids obtained from them by hydrolysis are assigned a *trans*-configuration. Unlike coumarin the α-pyronoxanthones were stable in refluxing 2N-sodium hydroxide or ethanolic sodium ethoxide.

## Experimental

*2-Hydroxyxanthone.*—2-Carboxy-4′-methoxydiphenyl ether was obtained according to the method of Ullmann and Zlokasoff [12] in 30% yield. A 50% yield resulted when *o*-chlorobenzoic acid (62·4 g.) was condensed with *p*-methoxyphenol (59·6 g.) in hot pentyl alcohol (320 ml.), potassium carbonate (122 g.), and copper bronze (0·4 g.) for 5 hr. With *o*-fluorobenzoic acid in place of the chloro-acid no reaction occurred. The ether (35 g.) was first dissolved in acetyl chloride (350 ml.) and concentrated sulphuric acid (5·7 ml.), and most of the acetyl chloride (250 ml.) was then removed by distillation. On addition of water to the residue, 2-methoxyxanthone (30·5 g., 94%), m. p. 131°, separated. The ether was also cyclised by polyphosphoric acid at 100° in 1 hr., giving 2-methoxyxanthone (84%). Treatment of a solution of 2-methoxyxanthone in xylene with anhydrous aluminium chloride on a water-bath gave a quantitative yield of 2-hydroxyxanthone, m. p. 235—236° (von Kostanecki and Rutishauser [1] give m. p. 231°).

*2-Acetonyloxyxanthone.*—A mixture of 2-hydroxyxanthone (4·2 g.), redistilled chloroacetone (2·2 g.), and anhydrous potassium carbonate (13·8 g.) in anhydrous acetone (100 ml.) was heated under reflux and agitated for 5 hr. From the filtrate of the mixture *2-acetonyloxyxanthone* (3·6 g., 70%) was obtained as needles, m. p. 150—151° (from ethanol). It gave a positive iodoform test (Found: C, 71·3; H, 4·5. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%). Its 2 : 4-*dinitrophenylhydrazone* crystallised as yellow needles (from ethylene chloride), m. p. 225° (Found: C, 59·4; H, 3·6. $C_{22}H_{16}O_7N_4$ requires C, 58·9; H, 3·6%). 2-Acetonyloxyxanthone was cyclised neither by concentrated sulphuric acid at room temperature, nor under reflux in acetic acid containing a few drops of concentrated sulphuric acid. In the former case only starting material was recovered, in the latter de-etherification occurred.

[9] Campbell, McCallum, and Mackenzie, *J.*, 1957, 1922.
[10] Shah and Shah, *J. Univ. Bombay*, 1938, **7**, Pt. 3, 213.
[11] Canter and Robertson, *J.*, 1931, 1876.
[12] Ullmann and Zlokasoff, *Ber.*, 1905, **38**, 2111.

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1-*Formyl*-2-*hydroxyxanthone*.—(a) *By a Duff reaction.* 2-Hydroxyxanthone (21·2 g.), hexamine (98 g.), and acetic acid (800 ml.) were heated on a steam-bath for 7 hr. After addition of boiling aqueous hydrochloric acid (1 : 1; 400 ml.) the mixture was kept under reflux for 10 min., then poured into water (4 l.) and set aside overnight. Crystallisation of the precipitate from light petroleum (b. p. 100—120°) gave 1-*formyl*-2-*hydroxyxanthone* (8·1 g., 34%) as pale yellow needles, m. p. 163° (Found: C, 70·0; H, 3·0. $C_{14}H_8O_4$ requires C, 70·0; H, 3·4%). It gave a red colour with ethanolic ferric chloride and a 2 : 4-*dinitrophenylhydrazone*, m. p. 295° (from anisole), as orange needles (Found: N, 13·7. $C_{20}H_{12}O_7N_4$ requires N, 13·3%).

(b) *By a Reimer–Tiemann reaction.* 2-Hydroxyxanthone (1·0 g.),* sodium hydroxide (1·4 g.), chloroform (2·1 ml.), and water (30 ml.) were heated under reflux with stirring for 4 hr. The precipitate obtained by driving off the solvent and acidifying the aqueous suspension with dilute hydrochloric acid yielded on extraction with light petroleum (b. p. 100—120°) the aldehyde (16%), m. p. and mixed m. p. 163°.

2-*Acetoxy*-1-*formylxanthone*, obtained as white needles, m. p. 186°, by boiling a solution of 1-formyl-2-hydroxyxanthone in acetic anhydride–pyridine for 2 hr., crystallised from ethanol (Found: C, 68·4; H, 3·8. $C_{16}H_{10}O_5$ requires C, 68·1; H, 3·6%), had a negative ferric reaction, and gave a yellow precipitate with Brady's reagent.

1 : 2-*Dihydroxyxanthone*.—To 1-formyl-2-hydroxyxanthone (1·2 g.), pyridine (10 ml.), sodium hydroxide (0·4 g.), and water (5 ml.), hydrogen peroxide (6% w/v; 11·3 ml.) was added during 0·5 hr. with shaking. By addition of dilute hydrochloric acid (1 : 1; 50 ml.) 1 : 2-*dihydroxyxanthone* was obtained (1·04 g., 91%), crystallising as yellow needles (from aqueous ethanol), m. p. 166—167° (Found: C, 68·7; H, 3·6. $C_{13}H_8O_4$ requires C, 68·4; H, 3·5%). It gave a dark green ethanolic ferric reaction.

For various *derivatives* see the Table.

*Substituted* 1 : 2-*dihydroxyxanthones.*

| Xanthone | M. p. | Found (%) C | Found (%) H | Formula | Required (%) C | Required (%) H | Ethanolic $FeCl_3$ |
|---|---|---|---|---|---|---|---|
| 1 : 2-Diacetoxy | 190° | 64·9 | 3·9 | $C_{17}H_{12}O_6$ | 65·4 | 3·9 | — |
| 1 : 2-Dimethoxy | 130 | 70·4 | 4·9 | $C_{15}H_{12}O_4$ | 70·3 | 4·7 | — |
| 1 : 2-Methylenedioxy | 212 | 70·3 | 3·3 | $C_{14}H_8O_4$ | 70·0 | 3·4 | — |
| 2-Acetoxy-1-hydroxy [a] | 191 | 66·8 | 3·7 | $C_{15}H_{10}O_5$ | 66·6 | 3·7 | Dark green |
| 2-Acetoxy-1-methoxy [b] | 148 | 67·6 | 4·2 | $C_{16}H_{12}O_5$ | 67·6 | 4·3 | — |
| 2-Hydroxy-1-methoxy [c] | 171 | 69·0 | 4·6 | $C_{14}H_{10}O_4$ | 69·4 | 4·2 | — |
| 1-Hydroxy-2-methoxy [d] | 158 | 69·4 | 4·3 | $C_{14}H_{10}O_4$ | 69·4 | 4·2 | Dark green |
| 1-Acetoxy-2-methoxy | 144 | 67·6 | 4·3 | $C_{16}H_{12}O_5$ | 67·6 | 4·3 | — |
| 2-Benzyloxy-1-hydroxy [e] | 147 | 75·6 | 4·6 | $C_{20}H_{14}O_4$ | 75·5 | 4·4 | Dark green |
| 1 : 2-Dibenzyloxy | 126 | 78·9 | 5·1 | $C_{27}H_{20}O_4$ | 79·4 | 4·9 | — |

[a] Made by the pyroboroacetate method. [b] On admixture with 1-acetoxy-2-methoxyanthone the m. p. was depressed. [c] Obtained by hydrolysis of 2-acetoxy-1-methoxyxanthone with 2N-sodium hydroxide. [d] Prepared from equimolar quantities of dimethyl sulphate and 1 : 2-dihydroxyxanthone. [e] Obtained from equimolar quantities of benzyl bromide and 1 : 2-dihydroxyxanthone.

2-*Hydroxy*-9-*oxo*-1-*xanthylaldazine*.—Hydrazine sulphate (0·16 g.) and sodium acetate (0·54 g.) were boiled with 1-formyl-2-hydroxyxanthone (0·24 g.) in the minimum amount of ethanol for 5 min. Crystallisation of the yellow precipitate from anisole gave the *aldazine* (0·2 g.) as yellow needles, m. p. 365° (decomp.) (Found: C, 70·7; H, 3·4; N, 5·7. $C_{28}H_{16}O_6N_2$ requires C, 70·6; H, 3·4; H, 5·9%).

*Ethyl* 1-*Formyl*-9-*oxo*-2-*xanthyloxyacetate*.—1-Formyl-2-hydroxyxanthone (4·8 g.), ethyl bromoacetate (10·0 g.) and anhydrous potassium carbonate (16·6 g.) in anhydrous acetone (125 ml.) were kept under reflux for 14 hr. The filtrate obtained from the initially orange but finally pale yellow mixture deposited *ethyl* 1-*formyl*-9-*oxo*-2-*xanthyloxyacetate* (62%) as white needles, m. p. 143°, on evaporation (Found: C, 66·4; H, 4·4. $C_{18}H_{14}O_6$ requires C, 66·3; H, 4·3%). Hydrolysis with aqueous sodium hydroxide yielded the corresponding *acid*, m. p. 221° (Found: C, 64·5; H, 3·6. $C_{16}H_{10}O_6$ requires C, 64·4; H, 3·4%).

*Furano*(3′ : 2′-1 : 2)*xanthone*-5′-*carboxylic Acid*.—(*a*) Cyclisation of 1-formyl-9-oxo-2-xanthyloxyacetic acid (1·2 g.) was carried out with fused sodium acetate (3·0 g.) in boiling acetic anhydride for 2 hr. Addition of water (120 ml.), followed by neutralisation with sodium hydrogen carbonate, gave a precipitate which on recrystallisation from acetic acid yielded

*furano*(3′ : 2′-1 : 2)*xanthone-5′-carboxylic acid* as white needles (0·5 g., 45%), m. p. 322° (decomp.) (Found: C, 68·7; H, 2·8. $C_{16}H_8O_5$ requires C, 68·6; H, 2·9%). The acid is soluble in warm aqueous sodium hydrogen carbonate and sparingly soluble in cold dilute ammonia solution.

(*b*) A suspension of ethyl 1-formyl-9-oxo-2-xanthyloxyacetate (0·66 g.) in ethanol (35 ml.) containing sodium ethoxide (0·15 g.) was agitated for 1·5 hr. A pale yellow precipitate obtained by dilution with water (100 ml.) yielded on crystallisation from ethyl acetate 5′-*ethoxycarbonylfurano*(3′ : 2′-1 : 2)*xanthone* as white needles (56%), m. p. 207° (Found: C, 70·2; H, 4·0. $C_{18}H_{12}O_5$ requires C, 70·1; H, 3·9%). Hydrolysis of the ester with 4% ethanolic sodium hydroxide yielded the acid (88%) whose mixed m. p. with a sample from (*a*) was undepressed.

*Furano*(3′ : 2′-1 : 2)*xanthone*.—(*a*) Evaporation of the acetic acid mother-liquor from which the acid was obtained in the above experiment (*a*) left a residue which afforded *furano*(3′ : 2′-1 : 2)*xanthone* as white needles (0·25 g., 27%), m. p. 144° (Found: C, 76·0; H, 3·4. $C_{15}H_8O_3$ requires C, 76·2; H, 3·4%).

(*b*) Heating furano(3′ : 2′-1 : 2)xanthone-5′-carboxylic acid (0·28 g.) in quinoline (5 ml.) with copper bronze (0·28 g.) under reflux for 10 min. gave the furanoxanthone (0·12 g.), m. p. and mixed m. p. 144°.

6′-*Pyrono*(3′ : 2′-1 : 2)*xanthone*.—1-Formyl-2-hydroxyxanthone (4·8 g.), freshly fused sodium acetate (1·64 g.), and acetic anhydride (3·8 ml.) were heated for 2 hr. at 120° and then for a further 5 hr. at 180°. On trituration of the mixture with water a solid remained which yielded no extract on treatment with 2N-sodium hydroxide. On recrystallisation from acetic acid it afforded 6′-*pyrono*(3′ : 2′-1 : 2)*xanthone* as white needles (5·2 g.), m. p. 251° (Found: C, 72·7; H, 3·3. $C_{16}H_8O_4$ requires C, 72·7; H, 3·1%), not affected by ethanolic sodium ethoxide solution (cf. Updegraff and Cassidy [13]).

5′-*Methyl*-6′-*pyrono*(3′ : 2′-1 : 2)*xanthone*.—A Perkin reaction with 1-formyl-2-hydroxyxanthone (2·4 g.), sodium propionate (0·96 g.), and propionic anhydride (2·6 g.), as described in the previous experiment, gave 5′-*methyl*-6′-*pyrono*(3′ : 2′-1 : 2)*xanthone* (2·7 g., 97%) as white needles, m. p. 248° (Found: C, 73·7; H, 3·7. $C_{17}H_{10}O_4$ requires C, 73·4; H, 3·6%), unaffected by ethanolic sodium ethoxide.

trans-*Methyl* β-(2-*Methoxy*-9-*oxo*-1-*xanthyl*)*acrylate*.—To a suspension of 6′-pyrono(3′ : 2′-1 : 2)xanthone (0·5 g.) in boiling acetone (50 ml.) was added dimethyl sulphate (10 ml.) and 20% aqueous sodium hydroxide (22 ml.) in three portions during 0·5 hr. After 1 hour's refluxing the solvent was driven off and the solid obtained from the residue by acidification with dilute hydrochloric acid was recrystallised from aqueous ethanol. trans-*Methyl* β-(2-*methoxy*-9-*oxo*-1-*xanthyl*)*acrylate* had m. p. 135° (white needles) (Found: C, 69·2; H, 4·4. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%). Hydrolysis with ethanolic 2N-sodium hydroxide solution gave the *acid* as cream-coloured needles, m. p. 212° (Found: C, 69·4; H, 4·3. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%).

5′-Methyl-6′-pyrono(3′ : 2′-1 : 2)xanthone, treated as above, gave trans-*methyl* α-*methyl*-β-(2-*methoxy*-9-*oxo*-1-*xanthyl*)*acrylate* (47%), needles, m. p. 160° (Found: C, 70·0; H, 5·0. $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%); the derived *acid* formed pale-yellow needles, m. p. 208° (decomp.) (Found: C, 70·1; H, 4·5; OMe, 10·0. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·6; OMe, 10·0%).

We thank the Governors of the Royal Technical College, Salford, for a Research Demonstratorship (to F. L.).

ROYAL TECHNICAL COLLEGE, SALFORD, LANCS. [*Received, December 18th*, 1957].

[13] Updegraff and Cassidy, *J. Amer. Chem. Soc.*, 1949, **71**, 407.

XUM

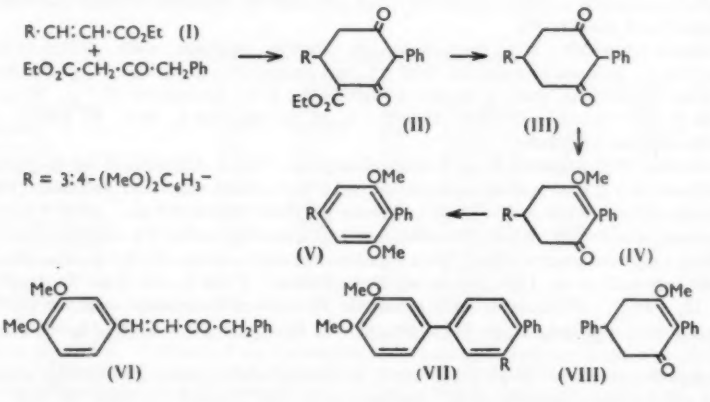
## 368. cyclo*Hexane*-1 : 3-*diones. Part IV.* The Synthesis of Further Terphenyl Derivatives.*

By G. R. Ames and W. Davey.

3 : 4-Di-, 3 : 4 : 3′-tri-, and 3 : 4 : 3′ : 5′-tetramethoxy-*p*-terphenyl have been prepared from 5-(3 : 4-dimethoxyphenyl)-2-phenyl*cyclo*hexane-1 : 3-dione. 4 : 5-Diphenyl*cyclo*hexane-1 : 3-dione has been converted into 3′ : 5′-dihydroxy- and 3′ : 5′-dimethoxy-*o*-terphenyl. Syntheses of 4′ : 6′-dihydroxy-*m*-terphenyl and of 2′ : 4′- and 4′ : 6′-dimethoxy-*m*-terphenyl are also described.

In Part II of this series [1] it was shown that dehydrogenation of compounds derived from 2 : 5-diphenyl*cyclo*hexane-1 : 3-dione afforded a new and convenient route to a number of *p*-terphenyls substituted in the central ring. This method has now been applied to the synthesis of *p*-terphenyls having methoxyl substituents in two rings, and also to *o*- and *m*-terphenyl derivatives

*Polymethoxy*-p-*terphenyls.*—The synthesis of terphenyl derivatives from 5-(3 : 4-dimethoxyphenyl)-2-phenyl*cyclo*hexane-1 : 3-dione (III) was examined. The dione was conveniently prepared by Michael addition of ethyl γ-phenylacetoactate to ethyl 3 : 4-dimethoxycinnamate (I), followed by hydrolysis of the dione-ester (II), and was converted




by diazomethane into the enol ether (IV). Dehydrogenation with sulphur, followed by treatment with dimethyl sulphate, then afforded 3 : 4 : 3′ : 5′-tetramethoxy-*p*-terphenyl (V) in 35% yield.

The alternative route to the dione-ester (II), namely addition of diethyl malonate to the unsaturated ketone (VI), was not examined as the latter could only be prepared in low yield and with difficulty.

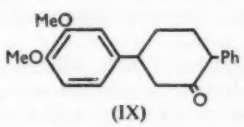
The enol ether (IV) was reduced with lithium aluminium hydride and then dehydrogenated with sulphur, to give 3 : 4-dimethoxy- (VII; R = H) (10%) and 3 : 4-dimethoxy-3′-hydroxy-*p*-terphenyl (VII; R = OH) (17%). The latter product was converted into the triether (VII; R = OMe) by treatment with dimethyl sulphate and alkali. The formation of the diether (VII; R = H) in the above reaction is analogous to that of *p*-terphenyl when the diphenyl enol ether (VIII) was reduced and dehydrogenated in the same way.[1]

* Part III, *J.*, 1958, 911.

[1] Ames and Davey, *J.*, 1957, 3480.

In an attempt to prepare 3 : 4-dimethoxy-*p*-terphenyl (VII; R = H) by an unambiguous route, the dione (III) was treated with phosphorus trichloride, and the product hydrogenated to the *cyclo*hexanone (IX). However, no crystalline product could be isolated when this ketone was reduced by the Wolff–Kishner method and the product dehydrogenated with selenium.

Attempts to prepare other diaryl*cyclo*hexane-1 : 3-diones by ethoxide-catalysed addition of ethyl γ-phenylacetoacetate to ethyl *m*-nitro-, *m*-benzamido-, or *o*-ethoxycarbonyl-cinnamate were unsuccessful. A convenient modification of the synthesis [2] of *o*-carboxycinnamic acid is described in the Experimental section.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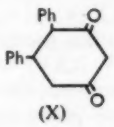
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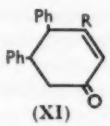
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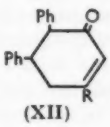
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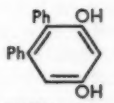
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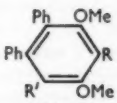
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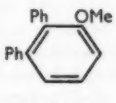
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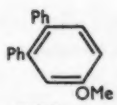
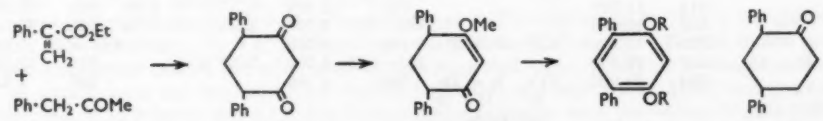

(XVI)

o-*Terphenyl Derivatives*.—4 : 5-Diphenyl*cyclo*hexane-1 : 3-dione [3] (X) with diazomethane gave a mixture of enol ethers, from which one, either (XI; R = OMe) or (XII; R = OMe), was obtained by repeated crystallisation. The mixed ethers were dehydrogenated with sulphur and then demethylated with hydriodic acid, to give 3′ : 5′-dihydroxy-*o*-terphenyl (XIII). Alternatively, treatment of the dehydrogenated material with dimethyl sulphate and alkali yielded the dimethoxy-compound (XIV; R = R′ = H), which, with two mols. of bromine, gave only a monobromo-derivative (XIV; R = Br, R′ = H or *vice-versa*).

Reduction of the purified enol ether by lithium aluminium hydride afforded the corresponding *cyclo*hexenone (XII or XI; R = H). Sulphur dehydrogenation of the latter gave an oil, which on treatment with dimethyl sulphate and alkali yielded 3′- (XV) or 4′-methoxy-*o*-terphenyl (XVI).

*Substituted* m-*Terphenyls*.—Two *cyclo*hexane-1 : 3-diones, (XVII) and (XXIII), are potential intermediates in the synthesis of *m*-terphenyl derivatives. The former, prepared by Michael addition of phenylacetone to ethyl atropate, was converted into the enol ether (XVIII) and thence into the resorcinol (XIX; R = H) and the diether (XIX; R = Me) by dehydrogenation and either demethylation or further methylation.


(XVII) (XVIII) (XIX) (XX)

No crystalline product was isolated in attempts to prepare the known [4] 4′-hydroxy-*m*-terphenyl from the enol ether (XVIII) by reduction with lithium aluminium hydride followed by sulphur dehydrogenation, or by selenium dehydrogenation of the ketone (XX),

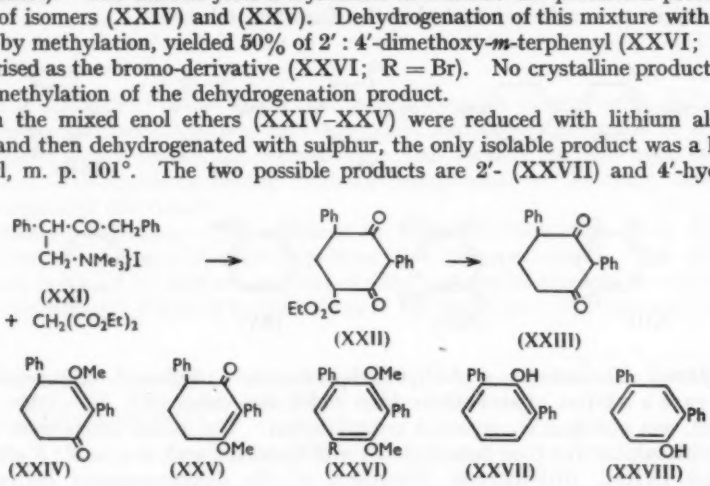
[2] *Org. Synth.*, 1954, **34**, 8.
[3] Borsche, *Ber.*, 1909, **42**, 4496.
[4] Lüttringhaus and Sääf, *Annalen*, 1945, **557**, 25.

XUM

which was prepared from the dione (XVII) by reaction with phosphorus trichloride, followed by catalytic hydrogenation.

Finally, 2 : 4-diphenyl*cyclo*hexane-1 : 3-dione (XXIII) was prepared by Robinson's modification [5] of the Michael reaction, from the methiodide (XXI) of the Mannich base [6] derived from dibenzyl ketone. Treating this compound with diethyl malonate in the presence of two mols. of sodium ethoxide gave an uncrystallisable acidic product, presumably the diketo-ester (XXII), which on hydrolysis with sodium carbonate afforded the dione (XXIII). This did not yield a crystalline enol ether: the product is presumably a mixture of isomers (XXIV) and (XXV). Dehydrogenation of this mixture with sulphur, followed by methylation, yielded 50% of 2′ : 4′-dimethoxy-*m*-terphenyl (XXVI; R = H), characterised as the bromo-derivative (XXVI; R = Br). No crystalline product resulted from demethylation of the dehydrogenation product.

When the mixed enol ethers (XXIV–XXV) were reduced with lithium aluminium hydride and then dehydrogenated with sulphur, the only isolable product was a hydroxyterphenyl, m. p. 101°. The two possible products are 2′- (XXVII) and 4′-hydroxy-*m*-




terphenyl (XXVIII); Lüttringhaus and Sääf [4,7] report that these compounds have m. p. 101° and 89° respectively. Our product is therefore regarded as the 2′-isomer (XXVII), and must be formed from the enol ether (XXIV).

| Compound | $\lambda_{max.}$ (mμ) | ε |
|---|---|---|
| II | 229 | 17,300 |
| | 282 | 17,200 |
| | *304* | 11,200 |
| III | 228 | 18,200 |
| | 272·5 | 14,800 |
| IV | 229 | 17,900 |
| | 274·5 | 14,700 |
| V | 281 | 24,100 |
| | 292 | 23,300 |
| VI | 244 | 11,200 |
| | *300* | 10,900 |
| | 339·5 | 19,800 |
| VII; R = H | *280* | 26,200 |
| | 296 | 28,900 |
| VII; R = OH | 277 | 20,600 |
| | 301 | 20,200 |
| VII; R = OMe | 277 | 21,800 |
| | 301 | 23,500 |
| X | 259·5 | 14,000 |
| | *290* | 6,990 |
| XI or XII; R = OMe | 251·5 | 18,500 |
| XIII | *226* | 23,900 |
| | *252* | 15,900 |
| | *285—300* | 4,100 |
| XIV; R = H | *246* | 19,200 |
| | *285—293* | 4,200 |
| XIV; R = Br, R′ = H or *vice versa* | 293 | 4,780 |
| XV or XVI | 223 | 27,200 |
| | *226* | 26,800 |
| XVII | 258 | 18,200 |
| | *290* | 6,460 |
| XVIII | 250 | 19,600 |
| XIX; R = H | 252 | 25,000 |
| | *274* | 14,300 |
| | 305 | 9,150 |
| XIX; R = Me | 248 | 26,200 |
| | 270 | 15,500 |
| | *293—300* | 8,720 |
| XXVI; R = H | 245 | 25,400 |
| XXVI; R = Br | 233 | 32,900 |
| | *285—292* | 2,360 |
| XXVII | 238 | 22,200 |
| | 295 | 4,820 |

The ultraviolet absorption spectra of most of the compounds described above are given in the Table, for 96% ethanol solutions, determined with a Unicam S.P. 500 Spectrophotometer. Italicised figures denote an inflexion.

[5] "Organic Reactions," Wiley, New York, 1942, Vol. I, p. 321.
[6] Wilson and Kyi, *J.*, 1952, 1321.
[7] Lüttringhaus and Sääf, *Annalen*, 1939, **542**, 241.

## Experimental

" Light petroleum " refers to the fraction of b. p. 60—80°.

*Ethyl* 6-(3 : 4-*Dimethoxyphenyl*)-2 : 4-*dioxo*-3-*phenyl*cyclo*hexanecarboxylate* (II).—To sodium (0·6 g.) in ethanol (50 c.c.) were successively added ethyl γ-phenylacetoacetate (5·2 g.) and ethyl 3 : 4-dimethoxycinnamate (11·8 g.), and the mixture refluxed for 6 hr. and then poured into water. After unchanged starting materials had been removed with ether, acidification yielded the *dione-ester* (1·8 g.), prisms, m. p. 158—159° (from benzene) (Found: C, 69·8; H, 6·4. $C_{23}H_{24}O_6$ requires C, 69·7; H, 6·1%).

5-(3 : 4-*Dimethoxyphenyl*)-2-*phenyl*cyclo*hexane*-1 : 3-*dione* (III).—The foregoing ester (17·4 g.) was refluxed for 10 hr. with sodium carbonate (decahydrate; 34·8 g.) in water (110 c.c.); the mixture was acidified and then brought to the boil. The *dione* (12·5 g.) was collected and recrystallised from 2-methoxyethanol: it formed needles, m. p. 220° (Found: C, 73·6; H, 6·1. $C_{20}H_{20}O_4$ requires C, 74·1; H, 6·2%).

5-(3 : 4-*Dimethoxyphenyl*)-3-*methoxy*-2-*phenyl*cyclo*hex*-2-*en*-1-*one* (IV).—Treatment of the above dione with ethereal diazomethane yielded the *enol ether*, prisms, m. p. 189°, from benzene (Found: C, 74·3; H, 6·3. $C_{21}H_{22}O_4$ requires C, 74·5; H, 6·5%).

3 : 4 : 3′ : 5′-*Tetramethoxy*-p-*terphenyl* (V).—The foregoing enol ether (1 g.) was heated at 270° for 2 hr. with sulphur (0·1 g.), and the product refluxed with dimethyl sulphate (2·1 c.c.) and 2N-sodium hydroxide (11 c.c.) for 2 hr., further quantities of the reagents (2·1 c.c. and 11 c.c. respectively) being added after 1 hr. After the excess of dimethyl sulphate had been destroyed, the product was collected and extracted with boiling light petroleum. From the extracts there separated 3 : 4 : 3′ : 5′-*tetramethoxy*-p-*terphenyl* (0·8 g.), plates, m. p. 127·5° (Found: C, 74·9; H, 6·2. $C_{22}H_{22}O_4$ requires C, 75·4; H, 6·3%).

1-(3 : 4-*Dimethoxyphenyl*)-4-*phenylbut*-1-*en*-3-*one* (VI).—Phenylacetone (6·7 g.), veratraldehyde (8·3 g.), and 2N-potassium hydroxide (6·7 c.c.) in water (500 c.c.) were heated at 70—90° for 2 days, more veratraldehyde (2·5 g.) and potassium hydroxide solution (6·7 c.c.) being added after one day. The aqueous layer was decanted and the residual oil taken up in methanol. The *ketone* (2·3 g., 16%) slowly separated (1—3 weeks): it crystallised from methanol as pale yellow plates, m. p. 89—90° (Found: C, 76·2; H, 6·4. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%).

3 : 4-*Dimethoxy*-p-*terphenyl* (VII; R = H) *and* 3′-*Hydroxy*-3 : 4-*dimethoxy*-p-*terphenyl* (VII; R = OH).—The enol ether (IV) (1·6 g.) in 1 : 2-dimethoxyethane (75 c.c.) was added during 10 min. to lithium aluminium hydride (0·2 g.) in the same solvent (25 c.c.). Working up in the usual way gave an oil which was heated with sulphur (0·16 g.) at 250—260° for 1 hr. Recrystallisation from ethanol afforded 3 : 4-*dimethoxy*-p-*terphenyl* (0·13 g.) as needles, m. p. 157° (Found: C, 82·5; H, 6·1. $C_{20}H_{18}O_2$ requires C, 82·7; H, 6·2%). Evaporation of the mother-liquors yielded 3 : 4-*dimethoxy*-3′-*hydroxy*-p-*terphenyl* (0·24 g.), needles, m. p. 173° (from benzene) (Found: C, 78·3; H, 5·7. $C_{20}H_{18}O_3$ requires C, 78·4; H, 5·9%).

3 : 4 : 3′-*Trimethoxy*-p-*terphenyl* (VII; R = OMe).—The preceding compound (0·12 g.) was refluxed for 2 hr. with dimethyl sulphate (2 c.c.) and 2N-sodium hydroxide (10 c.c.). The excess of dimethyl sulphate was destroyed with alkali and the product was collected. 3 : 4 : 3′-*Trimethoxy*-p-*terphenyl* formed needles, m. p. 103—104°, from light petroleum (Found: C, 78·7; H, 6·4. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%).

5-(3 : 4-*Dimethoxyphenyl*)-2-*phenyl*cyclo*hexanone*.—The dione (III) (7 g.) in chloroform (20 c.c.) was refluxed for 3 hr. with phosphorus trichloride (1·6 c.c.). To the cooled mixture were successively added ice, ethyl acetate, and saturated aqueous sodium hydrogen carbonate. The organic layer was washed with N-sodium hydroxide and with water, dried, and evaporated. The residue, in ethanol (250 c.c.), was shaken under hydrogen with palladous chloride (100 mg.) and triethylamine (10 c.c.). When absorption ceased, the catalyst was removed and the solution concentrated. 5-(3 : 4-*Dimethoxyphenyl*)-2-*phenyl*cyclo*hexanone* (3·4 g.) crystallised from methanol as the *hemihydrate*, needles, m. p. 109° (Found, after drying at 80°/0·1 mm.: C, 74·8; H, 7·1. $C_{20}H_{20}O_3,\frac{1}{2}H_2O$ requires C, 75·2; H, 7·3%). The *oxime*, needles from ethyl acetate, had m. p. 211—212° (Found: C, 73·6; H, 7·0; N, 4·2. $C_{20}H_{23}O_3N$ requires C, 73·8; H, 7·1; N, 4·3%).

*Ethyl* 3-*benzamidocinnamate*, prepared from the acid [•] by the Fischer–Speier method,

[•] Heller, *Ber.*, 1913, **46**, 3974.

formed needles, m. p. 124°, from ethanol (Found: C, 73·5; H, 5·7; N, 4·6. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8; N, 4·7%).

2-*Carboxycinnamic Acid*.—To β-naphthol (20 g.) in formic acid (*d* 1·2; 110 c.c.) was added 30% hydrogen peroxide (57 c.c.). After a few minutes an exothermic reaction began; the reaction was moderated by occasional cooling in an ice-bath, the temperature being allowed to rise slowly to 70°. After cooling, the product (15·6 g., 59%), m. p. 205—208°, was collected. Although the yield is somewhat lower, this method appears to be more convenient than the peracetic acid oxidation.[2]

*Synthesis of Diphenyl*cyclo*hexane*-1 : 3-*diones*.—The 4 : 5-isomer was prepared as described by Borsche.[3]

*Ethyl atropate*. The method described is an improvement on that of Schinz and Hinder.[3] Ethyl oxalate (109·5 g.) and ethyl phenylacetate (162·9 g.) were successively added to sodium ethoxide foam (from 17·4 g. sodium) in benzene (300 c.c.), and the mixture was set aside overnight. The sodium salt which separated was collected, washed with ether, and acidified. To the resulting oxalo-ester in 38% aqueous formaldehyde (90 c.c.) and water (300 c.c.) at 15°, was added, during 30 min., potassium carbonate (81 g.) in water (150 c.c.), and the mixture was stirred for 2 hr. Isolation with ether yielded ethyl atropate (116 g., 88%), b. p. 76—77°/1·2 mm., $n_D^{20}$ 1·5238 (lit., b. p. 124°/16 mm., $n_D^{16}$ 1·52605). Schinz and Hinder obtained a 44% yield.

4 : 6-*Diphenyl*cyclo*hexane*-1 : 3-*dione* (XVII). Phenylacetone (4·3 g.) and ethyl atropate (5·6 g.) were added to a solution of sodium (0·7 g.) in ethanol (20 c.c.), and the mixture was refluxed for 3 hr. An equal volume of water was added and the liquid was decanted and acidified, to give the *dione*, prisms, m. p. 161—163° (Found: C, 81·4; H, 6·1. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

2 : 4-*Diphenyl*cyclo*hexane*-1 : 3-*dione* (XXIII). To sodium (10·9 g.) in ethanol (800 c.c.) were added diethyl malonate (37·4 g.) and 2 : 4-diphenyl-3-oxobutyltrimethylammonium iodide [4] (96 g.), and the mixture was refluxed for 7 hr. and then set aside for 3 days. After concentration, water (1 l.) was added and the acidic product, isolated in the usual way, was refluxed for 8 hr. with sodium carbonate decahydrate (48 g.) in water (320 c.c.). The solution was acidified and again brought to the boil. The *dione* (20·4 g.) crystallised from benzene as prisms, m. p. 176—178° (Found: C, 81·5; H, 6·1%). When this experiment was first performed, the product had m. p. 156—157° (Found: C, 81·2; H, 5·9%). This material, which was not isolated from subsequent runs, decomposed to an oil on storage in a glass tube; it was presumably a metastable form of the dione of m. p. 176—178°.

*Enol Ethers*.—Treatment of the 4 : 5-diphenyl-dione in methanol with excess of ethereal diazomethane yielded an oil, which, on trituration with light petroleum and repeated recrystallisation from benzene–light petroleum, afforded an *enol ether*, plates, m. p. 137° (Found: C, 81·8; H, 6·7. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%). The *enol ether* similarly prepared from the 4 : 6-diphenyl-dione crystallised from benzene as prisms, m. p. 172° (Found: C, 81·9; H, 6·4%).

3′ : 5′-*Dihydroxy*-o-*terphenyl* (XIII; R = H).—The crude mixture of enol ethers (from 5·2 g. of the 4 : 5-diphenyl-dione) was heated at 260—270° with sulphur (0·5 g.). The product was refluxed for 6 hr. with hydriodic acid (*d* 1·7; 20 c.c.), then poured into water. Isolation of the acidic fraction furnished 3′ : 5′-*dihydroxy*-o-*terphenyl* (0·5 g.), plates, m. p. 145—146°, from benzene–light petroleum (Found: C, 82·0; H, 5·2. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%). 4′ : 6′-*Dihydroxy*-m-*terphenyl* (XIX; R = H), prisms, m. p. 130°, from benzene (Found: C, 82·3; H, 5·0%), was similarly prepared.

3′ : 5′-*Dimethoxy*-o-*terphenyl* (XIII; R = Me).—The mixture of enol ethers (from 10 g. of the 4 : 5-diphenyl-dione) was dehydrogenated as described in the preceding experiment. The product was refluxed for 2 hr. with dimethyl sulphate (20 c.c.) and 2N-sodium hydroxide (100 c.c.), more of these reagents (20 c.c. and 100 c.c. respectively) being added after 1 hr. Isolation with ether gave a fraction, b. p. 180—190°/0·5 mm. (3·4 g.), which, on trituration with light petroleum, yielded the *diether*, plates, m. p. 136—137° (Found: C, 82·6; H, 6·4. $C_{20}H_{18}O_2$ requires C, 82·7; H, 6·2%); bromination of this compound in carbon tetrachloride solution afforded a *monobromo-derivative*, prisms, m. p. 196—197° (from benzene–light petroleum) (Found: C, 65·2; H, 4·4; Br, 21·4. $C_{20}H_{17}O_2Br$ requires C, 65·0; H, 4·6; Br, 21·6%).

Similarly prepared were 4′ : 6′- (XIX; R = Me), blades, m. p. 99°, from methanol (Found: C, 83·0; H, 6·6%), and 2′ : 4′-*dimethoxy*-m-*terphenyl* (XXVI; R = H), plates, m. p. 124°, b. p. 161—164°/0·2 mm. from light petroleum (Found: C, 82·4; H, 6·3%). Bromination of the

[3] Schinz and Hinder, *Helv. Chim. Acta*, 1947, **30**, 1349.

latter furnished the *bromo-compound* (XXVI; R = Br), prisms, m. p. 131—132° (from light petroleum) (Found: C, 64·8; H, 4·8%).

4 : 5- or 5 : 6-*Diphenyl*cyclo*hex*-2-*en*-1-*one* (XI or XII; R = H).—To lithium aluminium hydride (0·24 g.) in ether (100 c.c.) was added the enol ether of the 4 : 5-diphenyl-dione (1·7 g.; m. p. 133—134°) in benzene (50 c.c.), and the mixture refluxed for 1 hr. Working up in the usual way afforded the *ketone*, prisms, m. p. 90°, from methanol (Found: C, 86·5; H, 6·5. $C_{18}H_{16}O$ requires C, 87·1; H, 6·5%).

3′- or 4′-*Methoxy*-o-*terphenyl* [(XV) or (XVI)].—The foregoing ketone was heated at 260—270° for 2 hr. with sulphur (0·2 g.), and the product treated with dimethyl sulphate and alkali as described above for 3′ : 5′-dimethoxy-*o*-terphenyl. The ether crystallised from methanol as blades, m. p. 110°, b. p. 181—183°/2·5 mm. (Found: C, 87·8; H, 5·9. Calc. for $C_{18}H_{14}O$: C, 87·8; H, 5·7%). Lüttringhaus and Sääf [7] give m. p. 101°.

2 : 4-*Diphenyl*cyclo*hexanone Oxime*.—The 4 : 6-diphenyl-dione (12·3 g.) in chloroform (25 c.c.) was refluxed with phosphorus trichloride (3·4 c.c.) for 3 hr. Ice, ether, and aqueous sodium hydrogen carbonate were then added and the organic layer was separated, washed with aqueous sodium hydroxide, dried, and evaporated. The residue in ethanol (250 c.c.) was shaken under hydrogen with palladous chloride (0·2 g.) and triethylamine (20 c.c.). Evaporation of the filtered solution gave an oil, which was treated with hydroxylamine in the usual way: the *oxime* (28%) formed needles, m. p. 210—211°, from ethyl acetate (Found: C, 81·5; H, 7·3; N, 5·2. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2; N, 5·3%).

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## 369. *The Chemistry of Fungi. Part XXXI.* The Structure of Rosenonolactone.*

By ADELAIDE HARRIS, ALEXANDER ROBERTSON, and W. B. WHALLEY.

Dehydrogenation of rosenonolactone, a metabolite of *Trichothecium roseum* Link, and of dihydro*iso*rosenonolactone gives 1 : 7-dimethyl- and 9-hydroxy-1 : 7-dimethyl-phenanthrene, a result which, in conjunction with the composition and properties of the lactones, shows that they are diterpenoid derivatives having the same nucleus. Rosenono- and *iso*rosenono-lactone and their derivatives are γ-lactones, an examination of which in conjunction with earlier work [1] enables provisional structures to be ascribed to the metabolite and its degradation products.

IN continuation of the investigation on rosenonolactone,[1] a metabolite from the mycelium of *Trichothecium roseum* Link, the empirical formula $C_{20}H_{28}O_3$ has been substantiated and the compound found to exhibit infrared absorption at 1786 cm.$^{-1}$, indicating that it is a γ-lactone. Further, from the formula it appeared that this lactone was in all probability a diterpene derivative, a view now substantiated by the production of 1 : 7-dimethyl- and 9-hydroxy-1 : 7-dimethyl-phenanthrene on dehydrogenation of the lactone with selenium. The formation of the phenanthrol (I) clearly indicates the position of the keto-group, which from the infrared absorption of rosenonolactone at 1724 cm.$^{-1}$ (in $CCl_4$) and 1721 cm.$^{-1}$ (Nujol) together with the ultraviolet spectrum ($\lambda_{max.}$ 289 mμ, log ε 1·6) is present in a six-membered ring, whilst the fact that dihydrorosenonolactone is a saturated compound provides collateral evidence that rosenonolactone is tricyclic and may be represented by the partial formula (II). Thus rosenonolactone may be regarded, for purposes of nomenclature as a derivative of the hypothetical, fully saturated hydrocarbon, rosane.

In a re-examination of the behaviour of rosenonolactone with 2N-alcoholic acid it has been found that this reagent converts the lactone into a mixture of the unchanged compound and *iso*rosenonolactone, which from the ultraviolet ($\lambda_{max.}$ 290 mμ, log ε 1·3) and

* Part XXX, *J.*, 1957, 4931.

[1] Robertson, Smithies, and Tittensor, *J.*, 1949, 879.

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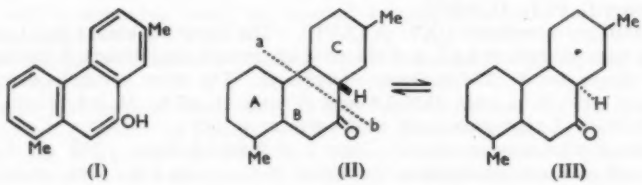
infrared (1712 and 1776 cm.$^{-1}$) absorption spectrum contains an isolated carbonyl group and a γ-lactone system; this reaction is reversible. The product previously designated *allo*rosenonolactone,[1] or compound (A), is not formed and the material thus described in the earlier communication [1] is a mixture difficult to separate; this has been resolved by




fractional crystallisation into rosenono- and *iso*rosenono-lactone. Accompanying *iso*rosenonolactone is a small quantity of a keto-dienoic acid, $C_{20}H_{28}O_3$, previously designated compound (B) [1] which exhibits only isolated carbonyl absorption in the ultraviolet spectrum ($\lambda_{max.}$ 286 mμ, log ε 1·89).

On reduction with potassium borohydride the carbonyl group of rosenonolactone gives rise to the corresponding secondary alcohol, rosenololactone, $C_{20}H_{30}O_3$ (infrared absorption at 3483 cm.$^{-1}$), which appears to be essentially stereochemically homogeneous, retains the γ-lactone system (infrared absorption at 1786 cm.$^{-1}$), forms an acetate, $C_{22}H_{32}O_4$, and regenerates rosenonolactone on oxidation with chromic oxide in pyridine. Similarly, on reduction *iso*rosenonolactone gives *iso*rosenololactone which retains the γ-lactone system (infrared absorption at 1783 cm.$^{-1}$) and is oxidised by chromic oxide in pyridine to *iso*rosenonolactone. When this reduction is effected at a temperature of *ca.* 50° *iso*rosenonolactone gives a mixture of *iso*rosenolo- and rosenolo-lactone, owing presumably to the conversion of some *iso*rosenononolactone into rosenonolactone before reduction since both rosenolo- and *iso*rosenolo-lactone are stable in the alkaline conditions which effect the interconversion of rosenono- and *iso*rosenono-lactone, a fact which clearly indicates that the keto-group is involved in the rosenono-⇌*iso*rosenono-lactone transformation. When heated with alcoholic hydrochloric acid, rosenololactone gives a high yield of an unsaturated hydroxy-acid, rosenolic acid (hydroxyrosenoic acid), $C_{20}H_{30}O_3$, by hydration of the γ-lactone system with simultaneous elimination of water, involving the liberated hydroxyl group which is probably tertiary. Similarly, *iso*rosenololactone furnishes *iso*rosenolic acid, $C_{20}H_{30}O_3$. Since on dehydrogenation with selenium both rosenono- and dihydro*iso*rosenono-lactone give 1 : 7-dimethylphenanthrene together with 9-hydroxy-1 : 7-dimethylphenanthrene it seems reasonably certain that rosenono- and *iso*rosenono-lactone have the same carbon skeleton and hence the difference between the normal and the *iso* series is probably stereochemical and of the type (II) ⇌ (III).

Condensation of either dihydrorosenono- or dihydro*iso*rosenono-lactone with ethanedithiol gave the same mercaptal, $C_{22}H_{34}O_2S_2$, which cannot, at this stage, be assigned to the normal or *iso* series, and it follows that the same ambiguity applies to the derivatives of this mercaptal. On desulphurisation with Raney nickel this compound furnished *iso*(?)hydroxyrosanoic lactone, $C_{20}H_{32}O_2$, devoid of ketonic properties and having a γ-lactone system (infrared absorption at 1779 cm.$^{-1}$). This lactone, which gives only 1 : 7-dimethylphenanthrene on dehydrogenation, forms a solution in hot alcoholic sodium hydroxide which remains clear on dilution with water and from which the unchanged compound was recovered on acidification 24 hours later, a result in agreement with the hypothesis that the carbonyl group is involved in the normal ⇌ *iso* series interconversion. On being heated with alcoholic hydrochloric acid or with naphthalene-2-sulphonic acid *iso*(?)hydroxyrosanoic lactone was converted in high yield into *iso*(?)rosenoic acid which, in view of its ultraviolet spectrum (log ε 3·39 at 214 mμ) and titration with perbenzoic acid

(which indicates one double bond), in conjunction with its failure to be hydrogenated under the standard conditions, appears to contain a tetrasubstituted double bond. The smooth decarboxylation of *iso*(?)rosenoic acid at the melting point indicates that the double bond is in the $\beta\gamma$-position to the carboxyl group. Methyl *iso*(?)rosenoate, $C_{21}H_{32}O_2$, is reduced with lithium aluminium hydride to *iso*(?)rosenol, $C_{20}H_{34}O$ (infrared absorption, 3322 cm.$^{-1}$ in Nujol), and on oxidation with *tert.*-butyl chromate this primary alcohol gave the corresponding aldehyde, *iso*(?)rosenal, which was isolated as the semicarbazone, $C_{21}H_{25}ON_3$. By Wolff–Kishner reduction this derivative gave the hydrocarbon, *iso*(?)rosene, $C_{20}H_{34}$, which on dehydrogenation furnished 1 : 7-dimethylphenanthrene in high yield, thereby establishing that the carboxyl group of rosenonolactone and hence of *iso*rosenonolactone occupies a tertiary position.

For convenience the acid, $C_{20}H_{30}O_5$, obtained by the oxidation [1] with potassium permanganate of sodium dihydro*iso*rosenonate, *i.e.*, a solution of dihydrorosenonolactone in aqueous sodium hydroxide, has been named rosoic acid. An investigation of the infrared spectrum of methyl rosoate in carbon tetrachloride indicates the presence of the following groups: $\gamma$-lactone (1783), ester (1748), and isolated ketone (1709 cm.$^{-1}$), in which the last assignment is confirmed by the ultraviolet absorption ($\lambda_{max.}$ 293—295 m$\mu$, log $\varepsilon$ 1·6). Reduction of methyl rosoate with potassium borohydride gives a dilactone, $C_{20}H_{30}O_4$, with infrared absorption at 1786 ($\gamma$-lactone) and 1745 cm.$^{-1}$ ($\varepsilon$-lactone) which is not cleaved by alkali, titrates as a dilactone, and is devoid of methoxyl and ketonic groups; methyl rosoate therefore cannot be a diketone. Rosoic acid, which is readily degraded by mild alkaline hydrolysis to a cyclic ketone $C_{10}H_{18}O$, and a dibasic keto-acid $C_{10}H_{18}O_5$,[1] is not readily decarboxylated and therefore unlikely to be a $\beta$-keto-acid. Since it appears reasonably certain that dihydro*iso*rosenonolactone contains a perhydrophenanthrene structure the combination of oxidation to rosoic acid and degradation of this with alkali must split the central ring B [as at line ab in (II)]. Further, since the Kuhn–Roth estimation shows that rosoic acid and dihydro*iso*rosenonolactone have the same *C*-methyl content it is clear that the formation of rosoic acid does not involve the conversion of a *C*-methyl group into a carboxyl group, but must occur by the scission of a carbon–carbon linkage of ring B in formula (II), and that the fission of the remaining link is effected by the alkali with the production of the two $C_{10}$ moieties. Moreover, since rosoic acid does not appear to be a $\beta$-keto-acid or a $\beta$-diketone, fission of the carbon–carbon bond with alkali is almost certainly a retro-aldol condensation and as rosoic acid is saturated the operative residue in this condensation must be of the type $\rangle C(OH)\cdot\overset{|}{C}\cdot CO\cdot$ and not $\cdot\overset{|}{C}\cdot\overset{|}{C}\cdot CO\cdot$.

On oxidation with nitric acid the cyclic ketone, $C_{10}H_{18}O$, derived from rosoic acid furnished $\alpha$-ethyl-$\alpha$-methylsuccinic acid, the specific rotation of which could not be determined with the quantity of acid available. The acid was however identified by its infrared absorption spectrum (in Nujol) [the same as that of ($\pm$)-$\alpha$-ethyl-$\alpha$-methylsuccinic acid]. Consequently, contrary to earlier views,[1] the succinic acid arises from a *gem*-methylvinyl residue in the ring of rosenonolactone giving rise to the $C_{10}H_{18}O$ ketone. This result in conjunction with the conversion of rosenonolactone into formaldehyde and an acid (carboxynorrosenonolactone), $C_{19}H_{26}O_5$, with ozone serves to establish the presence of the $\rangle CMe\cdot CH{=}CH_2$ system in the metabolite, and hence by analogy with the diterpenes of the dextropimaric acid series the partial structure (II) for rosenonolactone may be expanded to (IV).

The infrared absorption spectrum of the ketone $C_{10}H_{18}O$ shows the presence of a carbonyl group in a six-membered ring (1718 cm.$^{-1}$; film) consistent with the ultraviolet absorption spectrum ($\lambda_{max.}$ 283, log $\varepsilon$ 1·6) and with the oxidation of this ketone by ozone to a monobasic keto-acid $C_{10}H_{18}O_3$.[1] In contrast with the parent $C_{10}$ ketone this keto-acid gives an iodoform reaction, indicating the presence of a $CH_3\cdot CO\cdot$ group and hence the parent $C_{10}$ ketone must contain the residue $\cdot CO\cdot CHMe\cdot$.

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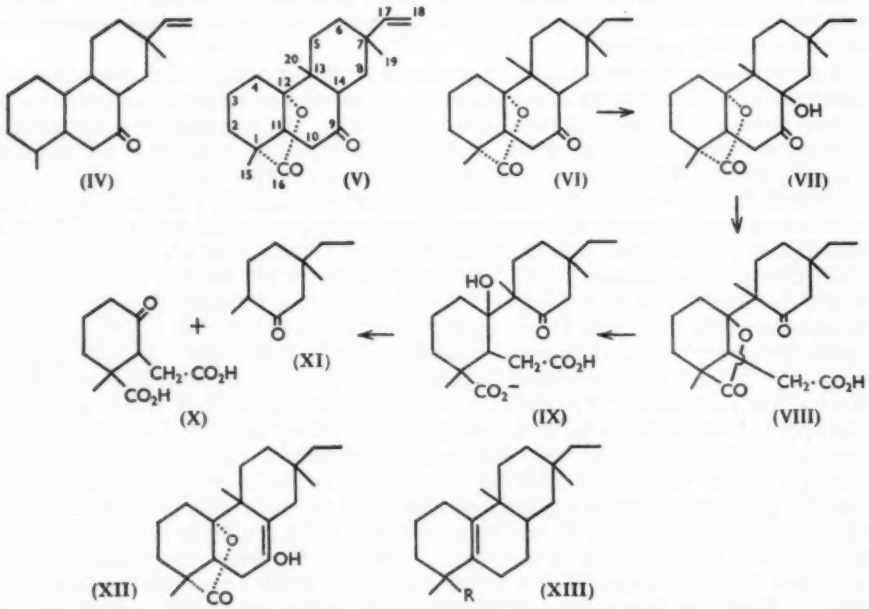
The $C_{10}$ dibasic keto-acid,[1] derived from rosoic acid, is substantially unaffected by neutral potassium permanganate solution and alkaline hydrogen peroxide and hence must be a saturated, cyclic compound. The carbonyl group, which is ketonic and not aldehydic, exhibits absorption in the ultraviolet region at $\lambda_{max.}$ 284—286 mμ (log ε 1·39) and in the infrared region at 1710 cm.$^{-1}$ (in Nujol), is unconjugated and hence must be present in a six-atom ring.

The foregoing experimental results together with earlier work [1] may be rationalised in terms of structure (V) for rosenonolactone and (VI) for dihydrorosenonolactone. On this

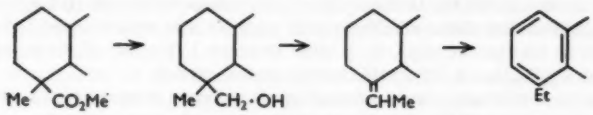



view the oxidation of sodium dihydro*iso*rosenonate probably proceeds by way of the α-ketol (VII) to rosoic acid (VIII) which in alkaline solution furnishes the anion (IX) with subsequent fission (retro-aldol condensation) of the β-hydroxy-ketone to give the $C_{10}$ cyclic ketone (XI) and the $C_{10}$ dibasic keto-acid (X); these structures agree with the general properties recorded for these substances in Part VI.[1] In accordance with the relative positions of the carboxyl groups in formula (X) and consequently in (IX) the acid (X) furnishes an anhydride. Formula (V) for rosenonolactone is also compatible with the rosenono–*iso*rosenono-lactone interconversion by way of the common enol (XII) (or its equivalent) but, whilst further definition of this change is required, it may be noted that the formation of enolic acetates [1] from *iso*rosenonolactone and dihydro*iso*rosenonolactone is significant in this connection. Furthermore, on the basis of the structure (VI) for dihydrorosenonolactone, *iso*(?)rosenoic acid may be represented as *iso*(?)ros-11 : 12-en-16-oic acid (XIII; R = $CO_2H$), *iso*(?)rosenol as *iso*(?)ros-11 : 12-en-16-ol (XIII; R = $CH_2$·OH) and *iso*(?)rosenal as *iso*(?)ros-11 : 12-en-16-al (XIII; R = CHO).*

The attachment of the third *C*-methyl residue to position 13 and of the carboxyl group to position 1 in formula (V) accords with the properties of rosenonolactone and its degradation products whilst the situation of the carboxyl residue is in agreement with the orientations of other natural diterpenoid acids, *e.g.*, abietic, vinhaticoic, and dextropimaric acid.

* The possibility that the double bond in these compounds occupies the 10 : 11- or (less probably) the 4 : 12-position cannot be excluded at this stage.

Moreover, from among the available tertiary locations for the carboxyl group, *viz.*, 1-, 11-, 12-, 13-, and 14-position in (V), allocation of the group to the 1-position appears to accommodate the experimental facts most satisfactorily. The divergence of formula (V) for rosenonolactone from the isoprene rule is not necessarily a valid objection since other diterpenes, *e.g.*, vouacapenic [2] and vinhaticoic acid,[3] do not conform to this principle. Attempts to substantiate the position of the carbonyl group in rosenonolactone by the following established reaction sequence [4] were unsuccessful:




Dehydration of *iso*(?)ros-11 : 12-en-16-ol furnished a conjugated heteroannular diene, $C_{20}H_{32}$ ($\lambda_{max.}$ 241, log $\varepsilon$ 3·7), which was catalytically hydrogenated to a mono-ethenoid hydrocarbon, $C_{20}H_{34}$, in which resistance to further saturation together with the light absorption (log $\varepsilon$ 3·66 at 216 mμ) indicate that the double bond is tetrasubstituted. On dehydrogenation this hydrocarbon, which may be a mixture, furnished a complex product from which a small quantity of 1 : 7-dimethylphenanthrene was isolated together with an aromatic polycyclic hydrocarbon having the properties and characteristic ultraviolet absorption spectrum of an anthracene.

Lactonisation of *iso*(?)ros-11 : 12-en-16-oic acid with sulphuric acid at −5° furnishes a saturated γ-lactone, *allo*hydroxyrosanoic lactone, $C_{20}H_{32}O_2$ (infrared absorption at 1779 cm.$^{-1}$), together with a very small quantity of a second isomeric γ-lactone, *neo*hydroxyrosanoic lactone (see the following paper), neither of which is identical with the isomeric hydroxy*iso*(?)rosanoic lactone derived from the mercaptal of dihydrorosenonolactone. No correspondence between these three lactones and the structurally associated γ-lactones derived from dextropimaric acid [5] has been established. Whilst the stereochemistry of rosenonolactone cannot be profitably discussed at this stage it seems probable that inversion of $C_{14}$ (formula V) occurs during the acid-catalysed lactonisation of (XIII; R = $CO_2H$) (cf. ref. 5) and that the 1-carboxyl and the 13-methyl group in the acid and hence in rosenonolactone are *cis*.

## Experimental

*Dehydrogenation of Rosenonolactone.*—Rosenonolactone [1] separated from alcohol–chloroform or from benzene in prisms, m. p. 208°, $[\alpha]_D^{13}$ −116° (*c* 2·0 in $CHCl_3$), $\lambda_{max.}$ 289 mμ (log $\varepsilon$ 1·6; log $\varepsilon$ 1·98 at 216 mμ) (Found: C, 75·9, 75·8; H, 9·0, 9·0. Calc. for $C_{20}H_{28}O_3$: C, 75·9; H, 8·9%). Robertson *et al.*[1] record m. p. 214°, $[\alpha]_D^{20}$ −107·5°. A mixture of the lactone (4 g.) and powdered selenium (8 g.) was kept at 320—330° for 48 hr., allowed to cool, and extracted with ether. The filtered ethereal solution was washed with N-sodium hydrogen carbonate (300 ml.), 2N-sodium hydroxide, and water, then dried and evaporated, leaving a partly crystalline residue which on purification by chromatography from light petroleum (b. p. 60—80°) on active aluminium oxide, followed by elution with the same solvent, gave 1 : 7-dimethylphenanthrene. This formed plates (0·68 g.), m. p. and mixed m. p. 85°, from methanol and gave a picrate, m. p. and mixed m. p. 132°.

Acidification of the aqueous sodium hydroxide extract gave a solid (0·15 g.). By the methyl sulphate–potassium carbonate method this gave a product which was purified by chromatography from light petroleum (b. p. 60—80°) on activated aluminium oxide. Concentration of the eluate gave 9-methoxy-1 : 7-dimethylphenanthrene, which separated from light petroleum (b. p. 60—80°) in plates (0·88 g.), m. p. and mixed m. p. 132°, having an infrared absorption spectrum identical with that of an authentic specimen (Found: C, 86·2; H, 6·5; OMe, 13·4. Calc. for $C_{16}H_{12}$·OMe: C, 86·4; H, 6·8; OMe, 13·1%).

Oxidation of the 9-methoxy-1 : 7-dimethylphenanthrene (0·2 g.) in acetic acid (2 ml.) with

[1] King, Godson, and King, *J.*, 1955, 1117.
[2] King and King, *J.*, 1953, 4158.
[4] Ruzicka, de Graaf, and Müller, *Helv. Chim. Acta*, 1932, **15**, 1300.
[5] Le-van-Thoi and Ourgaud, *Bull. Soc. chim. France*, 1955, 317.

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chromic oxide (0·3 g.) at 100° for 5 hr. furnished 1 : 7-dimethyl-9 : 10-phenanthraquinone which was condensed directly with *o*-phenylenediamine, yielding the requisite quinoxaline derivative,[6] m. p. and mixed m. p. 192° (Found: N, 8·9. Calc. for $C_{22}H_{14}N_2$: N, 9·1%).

iso*Rosenonolactone*.—A solution of rosenonolactone (1 g.) in alcohol (90 ml.) and hydrochloric acid (10 ml.) was heated under reflux for 2 hr., cooled, diluted with water (100 ml.), and basified with 2N-aqueous sodium hydroxide. The precipitate was isolated next day and on repeated crystallisation from methanol furnished, as the less soluble fraction, rosenonolactone (0·4 g.), m. p. and mixed m. p. 214°, with the requisite infrared absorption spectrum and specific rotation. The more soluble fraction consisted of *iso*rosenonolactone (0·1 g.), m. p. and mixed m. p. 144°. Acidification of the alkaline liquor gave an acid which separated from benzene or aqueous acetone in needles (50 mg.), m. p. 209° (decomp.) (Found: C, 75·7; H, 9·2%; equiv., 318·7. Calc. for $C_{20}H_{28}O_3$: C, 75·9; H, 8·9%; equiv., 316·4).

Under the same conditions *iso*rosenonolactone (1 g.) gave a mixture of rosenonolactone (0·2 g.), m. p. and mixed m. p. 214°, with the requisite infrared spectrum and specific rotation, and unchanged *iso*rosenonolactone (0·2 g.), plus the acid (50 mg.), m. p. and mixed m. p. 209°.

*Rosenololactone*.—When a solution of potassium borohydride (0·5 g.) in the minimum volume of water, containing 2 drops of 2N-sodium hydroxide, was added dropwise to rosenonolactone (1 g.) dissolved in methanol (200 ml.) at 35° (agitate), immediate effervescence occurred. Methanol was added as required to maintain a clear solution and 1 hr. later the mixture was diluted with water and the crystalline precipitate (0·9 g.) purified from benzene–chloroform, yielding *rosenololactone* in prisms (0·75 g.), m. p. 222° after softening at 218° (Found: C, 75·6; H, 9·6. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). A mixture of this alcohol (0·1 g.), 2N-aqueous sodium hydroxide (5 ml.), and ethanol (7 ml.) was heated under reflux for 1½ hr. On dilution with water (150 ml.) the cooled solution remained clear but subsequent acidification furnished a precipitate (0·09 g.) which on purification from methanol gave unchanged rosenololactone, m. p. and mixed m. p. 222° with softening from 218°. On oxidation by pyridine–chromic oxide for 12 hr. at 20° rosenololactone (0·5 g.) yielded rosenonolactone (0·4 g.), identical with an authentic specimen.

Prepared by the pyridine–acetic anhydride method, the *acetate* of rosenololactone separated from methanol in prisms, m. p. 186°, $[\alpha]_D^{20}$ +59·2° (*c* 0·15 in $CHCl_3$) (Found: C, 73·4; H, 9·1. $C_{22}H_{32}O_4$ requires C, 73·3; H, 9·0%), which on deacetylation with boiling 2N-aqueous sodium hydroxide (10 ml.) and alcohol (10 ml.) for 3 hr. regenerated the parent compound, m. p. and mixed m. p. 222°.

*Rosenolic Acid*.—A mixture of rosenololactone (0·5 g.), alcohol (90 ml.), and hydrochloric acid (10 ml.) was heated under reflux for 2 hr., cooled, basified with 2N-aqueous sodium hydroxide at 0°, extracted with ether, and acidified. The resulting precipitate was purified from acetone–light petroleum (b. p. 60—80°), giving *rosenolic acid* in needles (0·25 g.), m. p. 173°, $[\alpha]_D^{18}$ −97° (*c* 0·2 in $CHCl_3$) (Found: C, 75·5; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). The acid is readily soluble in sodium hydrogen carbonate solution, and in chloroform gives a yellow colour with tetranitromethane. There was almost no neutral fraction from this reaction.

iso*Rosenololactone*.—Prepared from *iso*rosenonolactone (1·0 g.) by reduction with potassium borohydride (0·5 g.) at room temperature, iso*rosenololactone* separated from methanol in needles (0·6 g.), m. p. 176°. On purification by chromatography from benzene solution on activated aluminium oxide this had m. p. 181° (Found: C, 75·1; H, 9·3. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%); admixed with rosenonolactone, it had m. p. *ca.* 128°. When the temperature of the reacting mixture was allowed to rise to *ca.* 50° the product was a mixture of rosenololactone, m. p. and mixed m. p. 222° (oxidised by chromic oxide–pyridine to rosenonolactone), and *iso*-rosenololactone, m. p. and mixed m. p. 181°, which was separated by fractional crystallisation. Boiled for 1½ hr. with alcohol (8 ml.) and 2N-aqueous sodium hydroxide (8 ml.), *iso*rosenololactone (0·1 g.) was recovered unchanged.

On oxidation with chromic oxide (0·25 g.) in pyridine the lactone (0·25 g.) regenerated *iso*-rosenonolactone (0·18 g.), m. p. and mixed m. p. 144°.

iso*Rosenolic Acid*.—A mixture of *iso*rosenololactone (1 g.), alcohol (90 ml.), and hydrochloric acid (10 ml.) was heated under reflux for 2 hr.; isolation of the acidic product in the usual manner gave iso*rosenolic acid*, needles (0·75 g.) (from aqueous methanol), m. p. 185°, $[\alpha]_D^{22}$ −138° (*c* 0·2 in $CHCl_3$) (Found: C, 75·5; H, 9·6%; equiv., 320. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%; equiv., 318·4). The neutral fraction from this reaction was negligible.

[6] Ruzicka and Waldmann, *Helv. Chim. Acta*, 1932, **15**, 907.

The *acetate* separated from aqueous methanol in needles, m. p. 153° (Found: C, 73·3; H, 9·1. $C_{22}H_{32}O_4$ requires C, 73·3; H, 9·0%).

*Dehydrogenation of Dihydroiso*rosenonolactone.—A mixture of dihydro*iso*rosenonolactone (6·0 g.) and powdered selenium (12·0 g.) was kept at 320—330° for 48 hr., then cooled and extracted with ether. The filtered extract was washed successively with N-aqueous sodium hydrogen carbonate and N-aqueous sodium hydroxide, dried, and evaporated, leaving a neutral fraction which, on purification by chromatography on activated aluminium oxide from light petroleum (b. p. 60—80°) with elution with the same solvent and crystallisation from methanol, gave 1 : 7-dimethylphenanthrene in plates (1·3 g.), m. p. and mixed m. p. 85° (Found: C, 93·2; H, 6·8. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%). The picrate separated from methanol in yellow needles, m. p. and mixed m. p. 130°.

Obtained by acidification of the aqueous sodium hydroxide extracts, the buff precipitate (0·65 g.) was methylated by methyl sulphate–potassium carbonate, and the product purified by chromatography from light petroleum (b. p. 60—80°) on activated aluminium oxide, giving 9-methoxy-1 : 7-dimethylphenanthrene in plates (0·5 g.), m. p. and mixed m. p. 132°, the ultraviolet absorption spectrum of which in alcohol exhibited max. at 217, 250, 257, 278, 300, 309, 338, 352 mμ (log ε 4·49, 4·65, 4·68, 4·24, 3·88, 3·84, 3·03, and 2·99 respectively) (Found: C, 86·2; H, 6·5; OMe, 13·4. Calc. for $C_{14}H_{13}$·OMe: C, 86·4; H, 6·8; OMe, 13·1%).

*Dihydroisorosenololactone.*—Reduction of dihydro*iso*rosenonolactone (1 g.) in methanol (5 ml.) with potassium borohydride (0·5 g.) in water (3 ml.), containing 2 drops of 2N-aqueous sodium hydroxide, for 1 hr. at 35° gave *dihydroisorosenololactone* which separated from methanol in needles, m. p. 163°, and was then purified by chromatography from benzene on activated aluminium oxide; this lactone had m. p. 166° (Found: C, 74·5; H, 9·6. $C_{20}H_{32}O_3$ requires C, 75·0; H, 10·1%). This (4·5 g.) with powdered selenium (9·0 g.) in the manner employed for dihydro*iso*rosenonolactone gave pimanthrene (0·8 g.), m. p. and mixed m. p. 85°, and 9-methoxy-1 : 7-dimethylphenanthrene (0·06 g.), m. p. and mixed m. p. 132°.

12-*Hydroxy*iso(?)*rosan*-16-*oic Lactone.*—A slow stream of hydrogen chloride was led into a solution of dihydro*iso*rosenonolactone (1 g.) in ethanedithiol (1·7 ml.) at 0° for 1 hr. and next day the partly crystalline mass was diluted with methanol. Recrystallised from benzene–ethanol, the *mercaptal* formed prisms (1 g.), m. p. 209°, $[\alpha]_D^{19}$ −38° (*c* 0·2 in $CHCl_3$) (Found: C, 67·0; H, 8·6. $C_{22}H_{34}O_2S_2$ requires C, 67·0; H, 8·6%). Dihydrorosenonolactone furnished the same mercaptal, m. p. and mixed m. p. 209°, having an identical infrared absorption spectrum.

A solution of this mercaptal (1 g.) in dioxan (20 ml.) and alcohol (30 ml.) containing Raney nickel (8·0 g.) was boiled for 60 hr., filtered, and evaporated, leaving a viscous oil which crystallised on trituration with light petroleum (b. p. 60—80°). Purification from methanol gave 12-*hydroxy*iso(?)*rosan*-16-*oic lactone* in needles (0·45 g.), m. p. 101° (Found: C, 79·1; H, 10·5. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%), $[\alpha]_D^{22}$ +51° (*c* 0·2). On dehydrogenation with powdered selenium (8 g.) at 320—330° for 48 hr. this compound (3·9 g.) gave pimanthrene (1·9 g.), m. p. and mixed m. p. 85°, which furnished the picrate, m. p. and mixed m. p. 131°; a phenolic product was not formed. A clear solution resulted when a mixture of 12-hydroxy*iso*-(?)rosan-16-oic lactone (0·5 g.), alcohol (7 ml.), and 2N-aqueous sodium hydroxide (7 ml.) was boiled for 45 min., cooled, and diluted with water (50 ml.). 24 Hr. later acidification of this gave the unchanged lactone (0·45 g.), m. p. and mixed m. p. 101° after purification.

iso(?)*Ros*-11 : 12-*en*-16-*oic Acid* [iso(?)*Rosenoic Acid*].—A solution of 12-hydroxy*iso*(?)rosan-16-oic lactone (1 g.) in alcohol (50 ml.) containing 2N-hydrochloric acid (50 ml.) was heated under reflux for 4 hr., cooled, diluted with water, and extracted with ether. The ethereal solution was washed with N-aqueous sodium hydroxide and the combined washings were acidified, giving iso(?)*ros*-11 : 12-*en*-16-*oic acid* which separated from aqueous methanol in plates (0·7 g.), m. p. 134°, $[\alpha]_D^{22}$ −146° (*c* 0·5 in $CHCl_3$) (Found: C, 79·0; H, 10·7%; equiv., 306. $C_{20}H_{32}O_3$ requires C, 78·9; H, 10·6%; equiv., 304·5). This compound is readily soluble in the common organic solvents and in 2N-aqueous hydrogen carbonate. There was no neutral fraction from this reaction.

The same acid was formed when a mixture of 12-hydroxy*iso*(?)rosan-16-oic acid lactone (1 g.) and naphthalene-2-sulphonic acid (0·08 g.) was melted on the steam-bath; the molten mixture crystallised after 5 min. A solution of this in ether was washed with N-aqueous sodium hydroxide, then with water, dried, and evaporated, leaving a negligible residue. Acidification of the alkaline extract gave *iso*(?)ros-11 : 12-en-16-oic acid (0·8 g.), m. p. and mixed m. p. 134°

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after purification from methanol. Prepared with diazomethane, the *methyl ester* had b. p. 172°/0·5 mm., m. p. *ca.* 33° (Found: C, 79·1; H, 10·9; OMe, 9·8. $C_{20}H_{31}O{\cdot}OMe$ requires C, 79·2; H, 10·8; OMe, 9·7%).

When heated at 200° in a sealed tube for 1½ hr. *iso*(?)rosenoic acid (25 mg.) furnished a neutral oily *substance* (15 mg.) which was purified by distillation and had no hydroxyl or carbonyl infrared absorption (Found: C, 86·3; H, 11·9. $C_{19}H_{32}$ requires C, 87·6; H, 12·4%).

*iso*(?)Ros-11 : 12-en-16-oic acid (0·15 g.) was added to concentrated sulphuric acid (3 ml.) at −10° and the stirred mixture was kept at −5° to −10° for ¾ hr. After addition of crushed ice the product was isolated with ether and purified from methanol, to give allo*hydroxyrosanoic lactone* in prisms (65 mg.), m. p. 138°, $[\alpha]_D^{21}$ +26·7° (*c* 0·08), with a negative tetranitromethane reaction in chloroform (log ε 1·93 at 214 mμ). Dilution of the methanolic mother-liquors with water gave a semisolid product which was purified from methanol, to give *neo*hydroxyrosanoic lactone (3 mg.) identical with the product from rosololactone (see following paper).

iso(?)*Rosen-16-ol*.—A solution of methyl *iso*(?)ros-11 : 12-en-16-oate (7 g.) in ether (250 ml.) was added gradually to a slurry of lithium aluminium hydride (4 g.) in ether (200 ml.); the mixture was heated under reflux for 72 hr., the excess of reducing agent was destroyed with ethyl acetate, and the ethereal solution was washed with 2N-sulphuric acid (300 ml.), water, dried, and evaporated, leaving iso(?)*ros*-11 : 12-*en*-16-*ol* which separated from methanol in needles (4·1 g.), m. p. 115°, $[\alpha]_D^{22}$ −103° (Found: C, 82·4; H, 11·4. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%). This was insoluble in 2N-aqueous sodium hydroxide and gave a yellow tetranitromethane reaction in chloroform. On being slowly heated at 0·35 mm. a mixture of this alcohol (5 g.) and naphthalene-2-sulphonic acid (0·1 g.) reacted at 160° and an oil (3 g.) rapidly distilled. A solution in ether of the product (5·7 g.), from two experiments, was washed with 2N-aqueous sodium hydroxide, dried, and distilled, furnishing a *product* as an oil (4·8 g.), b. p. 140—144°/0·3 mm., $\lambda_{max.}$ 241 mμ (log ε 3·7), $n_D^{24}$ 1·519, which gave an orange tetranitromethane reaction in chloroform (Found: C, 88·5; H, 11·9. $C_{20}H_{32}$ requires C, 88·2; H, 11·8%). Hydrogenation of this compound (12 g.) in ethyl acetate (280 ml.) with a catalyst (from 2 g. of palladium chloride and 1 g. of charcoal) occurred in 2 hr. (900 c.c., 1 mol. absorbed), giving a *hydrocarbon* (11·0 g.), b. p. 138—140°/0·5 mm. (log ε 3·66 at 216 mμ), $n_D^{24}$ 1·510, which had a yellow tetranitromethane reaction in chloroform (Found: C, 87·9; H, 12·3. $C_{20}H_{34}$ requires C, 87·5; H, 12·5%).

On dehydrogenation with selenium (22 g.) at 330—340° for 60 hr. followed by isolation of the product with ether and preliminary purification from light petroleum (b. p. 60—80°) on aluminium oxide this hydrocarbon (11 g.) gave an oil (5·0 g.), b. p. 140—160°/0·1 mm., which was separated arbitrarily into four fractions. Fractions 2, 3, and 4 deposited a colourless solid which was isolated after dilution with alcohol and purified from benzene–light petroleum (b. p. 60—80°), yielding an *anthracene derivative* in plates (25 mg.), m. p. 240°, $\lambda_{max.}$ 227, 257, 343, 357, and 378 mμ ($E_{1\,cm.}^{1\%}$ 2·8, 3·91, 2·26, 2·31, and 218 respectively) (Found: C, 93·0; H, 7·4; *C*-Me, 6·0. $C_{17}H_{14}$ requires C, 92·7; H, 7·3; 3*C*-Me, 20·4. $C_{16}H_{14}$ requires C, 93·2; H, 6·8; 2*C*-Me, 14·5%). The combined fractions were treated with picric acid. Prolonged fractional crystallisation of the resulting picrates, followed by conversion into the trinitrobenzene derivatives and then regeneration of the picrates, ultimately furnished 1 : 7-dimethylphenanthrene picrate (80 mg.), m. p. and mixed m. p. 132°. The remaining picrates (1·3 g.) appeared to consist essentially of that of 1 : 7-dimethylphenanthrene.

iso(?)*Rosene*.—*iso*(?)Ros-11 : 12-en-16-ol (1 g.) dissolved in benzene (8 ml.) was oxidised with *tert.*-butyl chromate (from 0·8 g. of chromic oxide, 4 ml. of benzene, and 4 ml. of *tert.*-butyl alcohol) at 25° for 7 days and the resulting black precipitate decomposed by the addition of ether and water containing sulphur dioxide, giving *iso*(?)ros-11 : 12-en-16-al as a neutral oil which exhibited carbonyl absorption (1715 $cm.^{-1}$ in Nujol). The *semicarbazone* separated from methanol in needles (0·67 g.), m. p. 230° (Found: C, 73·0; H, 10·2; N, 12·4. $C_{21}H_{35}ON_3$ requires C, 73·0; H, 10·2; N, 12·2%).

A mixture of this semicarbazone (6 g.), sodium (4 g.), diethylene glycol (70 ml.), and hydrazine hydrate (0·75 ml.) was heated under reflux at 233° for 10 hr., then poured into water. Isolated with ether, the resulting iso(?)*rosene* separated from alcohol in needles (4 g.), m. p. 59° (Found: C, 87·2; H, 12·7. $C_{20}H_{34}$ requires C, 87·5; H, 12·5%). Dehydrogenation of this hydrocarbon (3 g.) with selenium (6 g.) at 320—330° for 36 hr. gave 1 : 7-dimethylphenanthrene (1·4 g.), m. p. and mixed m. p. 85°, forming the picrate, m. p. and mixed m. p. 132°.

*Rosoic Acid*.—Prepared as described previously,[1] this acid had a negative ferric reaction and

was recovered unchanged when repeatedly heated above the m. p. Reduction of methyl rosoate (0·5 g.) in methanol (8 ml.) in 1 hr. by gradual addition of a solution of potassium borohydride (0·25 g.) in water (3 ml.), followed by acidification with 2N-hydrochloric acid, gave a *dilactone* which separated from methanol in needles (0·16 g.), m. p. 239°, mixed m. p. with rosoic acid 190—200° [Found: C, 71·7; H, 8·7%; OMe, 0. equiv., 173. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%; equiv. (dibasic), 167]. This product, which is insoluble in cold 2N-aqueous sodium hydroxide, has a negative tetranitromethane reaction in chloroform, and on being subjected to the conditions employed for the fission of rosoic acid is recovered unchanged.

*Oxidation of the* $C_{10}H_{18}O$ *Ketone* (With W. R. Smithies).—A vigorous reaction was initiated by heating a mixture of the ketone (1·8 g.), nitric acid (15 ml.), and water (15 ml.) on the steam-bath for *ca.* 5 min.; the oxidation was then allowed to proceed spontaneously. The mixture was next heated on the steam-bath for ½ hr., cooled, and diluted with water (30 ml.). The clear solution was decanted from the sticky residue and evaporated on the steam-bath, and the residual solid was extracted with chloroform–light petroleum (b. p. 60—80°), leaving a crystalline residue of oxalic acid (0·08 g.). Evaporation of the extract furnished an oil, b. p. 200—220°/760 mm., a solution of which in ether was washed with 2N-aqueous sodium hydrogen carbonate and then evaporated. The residual gum was warmed on the steam-bath with 2N-aqueous sodium hydroxide (10 ml.), and the resulting homogeneous solution acidified, giving (+)- or (−)-*α-ethyl-α-methylsuccinic acid* which separated from ether–light petroleum (b. p. 40—60°) in prisms (0·12 g.), m. p. 98° (Found: C, 52·7; H, 7·2. $C_7H_{12}O_4$ requires C, 52·5; H, 7·5%). The infrared absorption spectrum (in Nujol) and the potentiometric titration curve of this acid were identical with those of (±)-α-ethyl-α-methylsuccinic acid.[7]

Boiled with acetic anhydride for 2½ hr., the keto-acid [1] $C_{10}H_{14}O_5$ from rosoic acid gave a sticky solid which on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave the *anhydride* in large polyhedra, m. p. 95° (Found: C, 61·3; H, 6·3. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). Hydrolysis with warm 2N-aqueous sodium hydroxide regenerated the parent keto-acid, m. p. and mixed m. p. 203—204° (decomp.), in quantitative yield.

The ultraviolet absorption spectra were determined in 95% alcohol with a Unicam S.P. 500 Spectrophotometer and the infrared spectra in $CCl_4$ solution (unless stated to the contrary) with a Perkin-Elmer, Model 21, Spectrophotometer. The analyses were by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

University of Liverpool. [*Received, November 14th*, 1957.]

[7] Smith and Horwitz, *J. Amer. Chem. Soc.*, 1949, **71**, 3419.

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## 370. *The Chemistry of Fungi. Part XXXII.*[1] *Rosololactone, a Metabolite of* Trichothecium roseum *Link.*

By Adelaide Harris, Alexander Robertson, and W. B. Whalley.

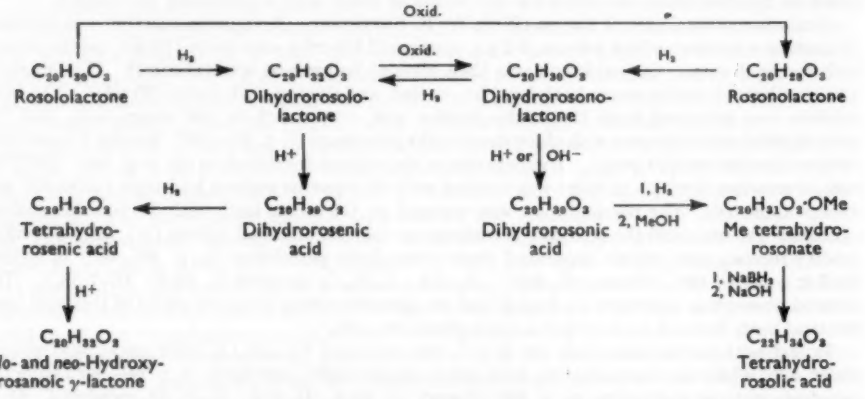
Rosololactone, $C_{20}H_{30}O_3$, from the mycelium of *T. roseum* Link, is a diterpenoid γ-lactone containing a secondary hydroxyl group and a vinyl residue and on dehydrogenation yields 1 : 7-dimethylphenanthrene. Dehydration of dihydrorosololactone readily gives a dienoic acid, dihydrorosenic acid, which on hydrogenation is converted into tetrahydrorosenic acid. Lactonisation of this acid yields a mixture of *allo*- and *neo*-hydroxyrosanoic γ-lactone identical with the two γ-lactones from *iso*(?)ros-11 : 12-en-16-oic acid (Part XXXI [1]), thereby establishing a close structural affinity between rosolo- and rosenono-lactone.

In addition to the major constituent, rosenonolactone, the mycelium of *Trichothecium roseum* Link contains a minor metabolite which in Part VI [2] was designated rosonolactone. The present communication details an investigation on the chemistry and structure of this compound which has the formula, $C_{20}H_{30}O_3$. Since the metabolite, which appears

[1] Part XXXI, preceding paper.
[2] Robertson, Smithies, and Tittensor, *J.*, 1949, 879.

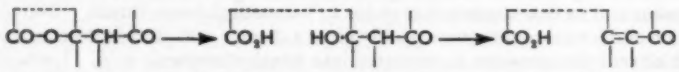
XUM

to be a γ-lactone (infrared absorption at 1776 cm.$^{-1}$), has no ketonic or aldehydic group but contains an alcoholic hydroxyl group, which can be acetylated, the trivial name rosonolactone has been changed to rosololactone, and the term rosonolactone transferred to the ketone, $C_{20}H_{28}O_3$, formed by the chromic oxide oxidation of the parent hydroxylactone which is thus a secondary alcohol. Rosonolactone is isomeric with rosenonolactone. Like rosenonolactone,[1] rosololactone contains a vinyl residue since ozonolysis



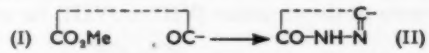

yields formaldehyde and carboxynor-rosololactone, $C_{19}H_{28}O_5$, and on hydrogenation gives the saturated dihydrorosololactone, $C_{20}H_{32}O_3$ (γ-lactone absorption at 1773 cm.$^{-1}$), which forms an acetate, $C_{22}H_{34}O_4$, and is oxidised to a keto-γ-lactone, dihydrorosonolactone, $C_{20}H_{30}O_3$ (infrared absorption at 1786 and 1730 cm.$^{-1}$), also obtained by hydrogenation of rosonolactone. Reduction of dihydrorosonolactone with potassium borohydride regenerates dihydrorosololactone (see chart). Dehydrogenation of rosololactone with selenium yields 1 : 7-dimethylphenanthrene, which, in conjunction with the fact that dihydrorosololactone is fully saturated, suggests that the lactone is a derivative of a tricyclic diterpene.

Whilst dihydrorosololactone is stable to 4N-aqueous sodium hydroxide its oxidation product dihydrorosonolactone is unstable to warm N-acid or -alkali, giving an unsaturated keto-acid, $C_{20}H_{30}O_3$, named dihydrorosonic acid. The ultraviolet absorption spectrum of dihydrorosonic acid ($\lambda_{max.}$ 248 mμ, log ε 4·0; $\lambda_{max.}$ 314 mμ, log ε 1·8) indicates that the compound is an αβ-unsaturated ketone whilst the ready formation of this acid (contrast the behaviour of rosenono- and dihydrorosenono-lactone [1]) provides strong evidence that the hydroxyl group, which is liberated by the hydrolysis of the lactone system in the precursor, is in the β-position to the carbonyl residue according to the scheme:




On dehydrogenation with sulphur or selenium, dihydrorosonic acid gave only 1 : 7-dimethylphenanthrene, indicating that skeletal changes do not occur in the transformations leading to this acid. Reduction of methyl dihydrorosonate with potassium borohydride furnished a γ-lactone (C) $C_{20}H_{30}O_2$ (infrared absorption at 1786 cm.$^{-1}$), derived from the precursor, methyl dihydrorosolate, by elimination of methanol. Hydrogenation of dihydrorosonic acid slowly gave the saturated keto-acid, tetrahydrorosonic acid, $C_{20}H_{32}O_3$ ($\lambda_{max.}$ 291 mμ, log ε 1·5), which yields an oxime, a 2 : 4-dinitrophenylhydrazone, a methyl ester, and a mercaptal with ethanedithiol. Attempts to form a hydrazone from methyl tetrahydrorosonate gave a non-acidic product, $C_{20}H_{32}ON_2$, devoid of a methoxyl group and having a molecule of methanol less than expected; the same compound was obtained

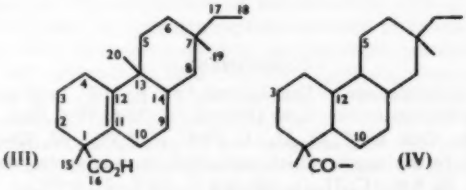
by Wolff–Kishner reduction of tetrahydrorosonic acid; its formation indicates the presence of the system (I) which yields a five-, six-, or seven-membered ring (II) (cf., *e.g.*, marrubiin [3]).



(I) (II)

Reduction with potassium borohydride of the keto-group in methyl tetrahydrorosonate gave the secondary alcohol, which, in contrast to the analogous product from methyl dihydrorosonate, did not readily lactonise.

When treated with naphthalene-2-sulphonic acid or boiling alcoholic hydrochloric acid, dihydrorosololactone gave a conjugated heteroannular dienoic acid, dihydrorosenic acid, $C_{20}H_{30}O_2$ ($\lambda_{max.}$ 238 mμ, log ε 4·15), which furnished 1 : 7-dimethylphenanthrene on dehydrogenation. Catalytic hydrogenation of this acid ceased after absorption of one mol., giving tetrahydrorosenic acid, $C_{20}H_{32}O_2$, which is probably a βγ-unsaturated acid since it readily undergoes decarboxylation at the melting point.



(III) (IV)

Reduction of methyl dihydrorosenate with lithium aluminium hydride gave the primary alcohol, dihydrorosenol, $C_{20}H_{32}O$, which on dehydration followed by dehydrogenation furnished a complex mixture from which there was isolated a small quantity of 1 : 7-dimethylphenanthrene together with the anthracene derivative obtained on dehydrogenation of the corresponding derivative of rosenonolactone.[1]

On lactonisation with sulphuric acid at −5° tetrahydrorosenic acid gave the isomeric saturated *allo*- and *neo*-hydroxyrosanoic γ-lactones, $C_{20}H_{32}O_2$, formed by the lactonisation [1] of *iso*(?)rosenoic acid [probably (III)] derived from rosenonolactone. The identity of the two pairs of lactones serves to establish that the carboxyl groups of rosenono- and rosololactone occupy corresponding positions; in rosenonolactone and thus also in rosololactone this group is probably such that its carbon atom is number 16 (cf. III).

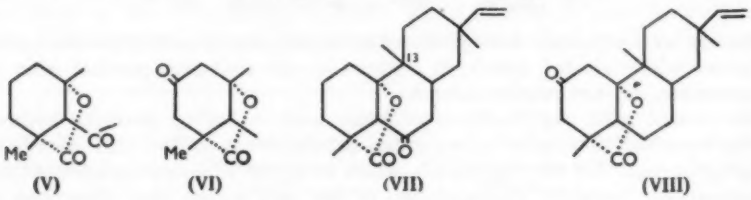
Further, from the relationship of *neo*- to *allo*-hydroxyrosanoic lactone together with the partial structure of rosenonolactone (preceding paper [1]), it is clear that dihydrorosololactone contains both a methyl and an ethyl group in the 7-position (see III). Because there is no reason to suspect that the conversion of either rosenono- or rosolo-lactone into *neo*- and *allo*-hydroxyrosanoic lactone is accompanied by inversion or migration at the 1- and 7-positions, the stereochemistry at $C_{(1)}$ and $C_{(7)}$ is identical in dihydrorosenono- and in dihydrorosolo-lactone and consequently dihydrorosolo-lactone may be represented by the partial formula (IV).

Now formation of the lactone (C) involves the secondary hydroxyl group formed by the reduction of the keto-group of the precursor, methyl dihydrorosonate. This hydroxyl group may occupy the position of the parent keto-group or, if an allylic shift intervenes, a β-position to it. In either case the γ-lactone must terminate at $C_{(3)}$, $C_{(10)}$, or $C_{(12)}$. The γ-lactone group in rosonolactone terminates on one of the same carbon atoms. Consequently, on the reasonable assumption that the potential hydroxyl group of the γ-lactone system in rosonolactone is in the β-position to the isolated keto group, the ketonic group of rosonolactone is situated at $C_{(3)}$ or $C_{(10)}$ and hence rosonolactone contains the system (V) or (VI), which is in accord with the formation of a cyclic derivative from

[3] Hardy, Rigby, and Moody, *J.*, 1957, 2955.

methyl tetrahydrorosonate and hydrazine. Further, the production of this derivative seems to exclude location of the ketonic residue at $C_{(5)}$.

These considerations together with the transformations and degradations described may be rationalised in terms of the structure (VII) or (VIII) for rosonolactone, in which




(V) (VI) (VII) (VIII)

the *C*-methyl group is placed at $C_{(13)}$ by analogy with the associated rosenonolactone;[1] alternative equivalent structures cannot be excluded at present.

## Experimental

*Dehydrogenation of Rosololactone.*—This lactone,[2] m. p. 186°, $[\alpha]_D^{18}$ +6·3° (*c* 2·3), log ε 2·25 at 210 mμ, from *Trichothecium roseum* Link [Found: C, 75·6, 75·5, 75·7, 75·2; H, 9·5, 9·4, 9·4, 9·4%; *M* (Rast), 324·6. Calc. for $C_{20}H_{32}O_3$: C, 75·4; H, 9·5%; *M*, 328], gave in boiling acetic anhydride–sodium acetate the *acetate* which separated from aqueous alcohol in needles, m. p. 167° (Found: C, 73·2; H, 8·9. $C_{22}H_{32}O_4$ requires C, 73·3; H, 9·0%).

The lactone (14 g.) was heated with powdered selenium (26 g.) at 320—330° for 36 hr., cooled, and extracted with ether. The extract was washed with 2N-aqueous sodium hydroxide, dried, and evaporated, leaving a residue which, on chromatography from light petroleum (b. p. 60—80°) on aluminium oxide followed by crystallisation from methanol, gave 1 : 7-dimethylphenanthrene in plates (5·8 g.), m. p. and mixed m. p. 85° (Found: C, 93·2; H, 7·1; *C*-Me, 9·3. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8; 2*C*-Me, 14·6%). The picrate had m. p. and mixed m. p. 132° (Found: C, 60·8; H, 3·9; N, 9·7. Calc. for $C_{22}H_{17}O_7N_3$: C, 60·7; H, 3·9; N, 9·7%), and the trinitrobenzene complex had m. p. and mixed m. p. 160° (Found: C, 62·9; H, 4·3; N, 10·0. Calc. for $C_{22}H_{17}O_6N_3$: C, 63·0; H, 4·1; N, 10·0%). The alkaline extract of the crude product did not yield phenolic material.

*Ozonolysis of Rosololactone.*—The lactone (1 g.), in chloroform (100 ml.) at 0°, was oxidised with ozone and oxygen for 40 min. and after the removal of the solvent in a vacuum the residual syrup was decomposed with water (150 ml.). Decanted from the solid product next day, the aqueous liquors were distilled into aqueous 2 : 4-dinitrophenylhydrazine sulphate, and the resulting formaldehyde 2 : 4-dinitrophenylhydrazone (0·25 g.) purified from alcohol, forming yellow needles, m. p. and mixed m. p. 161° (Found: N, 26·4. Calc. for $C_7H_6O_4N_4$: N, 26·7%). A solution of the solid in ether was extracted with N-aqueous sodium hydrogen carbonate and evaporated, leaving an intractable neutral fraction (0·3 g.). Acidification of the bicarbonate extracts furnished *carboxynor-rosololactone* which separated from alcohol in needles (0·4 g.), m. p. 286° (decomp.) (Found: C, 67·7; H, 8·4%; equiv., 316. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·4%; equiv., 336).

*Rosonolactone.*—A solution of chromic oxide (0·8 g.) in acetic acid (20 ml.) was added dropwise to rosololactone (2 g.) in acetic acid (40 ml.) at 45—50° in 30 min. and the cooled mixture neutralised with 2N-aqueous sodium carbonate. The resulting gummy precipitate was purified from alcohol and then benzene–light petroleum (b. p. 60—80°), giving *rosonolactone* in prisms (1 g.), m. p. 126°, $\lambda_{max.}$ 291 mμ (log ε 1·5) in 2N-aqueous sodium carbonate or 2N-aqueous sodium hydroxide (Found: C, 75·7, 75·8; H, 8·8, 8·8. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%). When this compound (0·1 g.) was warmed with 5% aqueous sodium hydroxide (40 ml.) at 100° for 20 min., the resulting clear yellow solution did not deposit a solid on cooling and dilution with water, but on subsequent acidification gave a precipitate of *rosonic acid* which separated from alcohol or ethyl acetate–light petroleum (b. p. 60—80°) in needles (0·04 g.), m. p. 161°, readily soluble in 2N-aqueous sodium hydrogen carbonate, $[\alpha]_D^{18}$ −118° (*c* 0·3) (Found: C, 75·8; H, 8·9%; equiv., 318. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%; equiv., 316).

On ozonolysis in chloroform, rosonclactone (1 g.) gave formaldehyde (isolated as the 2 : 4-dinitrophenylhydrazone) and *carboxynor-rosonolactone* which separated from aqueous alcohol in needles (0·1 g.), m. p. 271° (decomp.) (Found: C, 68·2; H, 8·0. $C_{19}H_{24}O_5$ requires C, 68·2; H, 7·8%).

*Dihydrorosololactone*.—In alcohol (150 ml.) containing a catalyst (from 0·1 g. of palladium chloride and 0·35 g. of charcoal) rosololactone (1·4 g.) absorbed 97 ml. (*ca.* 1 mol.) of hydrogen in 20 min. Reaction then ceased and the resulting *dihydrorosololactone* was isolated and purified from methanol, forming needles (1·2 g.), m. p. 183°, $[\alpha]_D^{18}$ +20° (*c* 3), which sublime unchanged at 212°/0·15 mm. and give a negative tetranitromethane or perbenzoic acid reaction (Found: C, 74·8; H, 10·0; *C*-Me, 8·3. $C_{20}H_{32}O_3$ requires C, 75·0: H, 10·1%). The solution formed by boiling dihydrorosololactone (0·5 g.) with aqueous-alcoholic (50% v/v) 4N-sodium hydroxide for 3 hr. remained clear on dilution with water, and acidification gave only the unchanged lactone (0·4 g.), m. p. and mixed m. p. 183° after purification. Boiling acetic anhydride–sodium acetate (2 hr.) gave the *lactone acetate*, needles (from alcohol), m. p. 160° (Found: C, 72·9; H, 9·4. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·5%); deacetylation regenerated the parent compound.

*Dihydrorosonolactone*.—(*a*) Hydrogenation of rosonolactone (0·5 g.) in alcohol (75 ml.) with palladium–charcoal (1 mol. of hydrogen rapidly absorbed in 15 min.) gave *dihydrorosonolactone* which separated from methanol and then benzene–light petroleum (b. p. 60—80°) in needles (0·4 g.), m. p. 138° (Found: C, 75·3; H, 9·4. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). The *oxime* formed needles, m. p. 222° (decomp.), from methanol (Found: C, 71·7; H, 9·3; N, 4·1. $C_{20}H_{31}O_3N$ requires C, 72·0; H, 9·4; N, 4·2%).

(*b*) Oxidation of dihydrorosololactone (1 g.) in acetic acid (20 ml.) with chromic oxide (0·4 g.) in acetic acid (10 ml.) at 40° gave dihydrorosonolactone (0·7 g.), forming needles, m. p. and mixed m. p. 138°, $\lambda_{max.}$ 295 mμ (log ε 1·4) (Found: C, 75·5; H, 9·5%). Reduction of dihydrorosonolactone (0·6 g.), dissolved in methanol (10 ml.), with a solution of potassium borohydride (0·3 g.) in water (2 ml. containing 1 drop of 2N-aqueous sodium hydroxide) added dropwise in 1 hr. regenerated dihydrorosololactone in needles (0·4 g.) which on purification from aqueous methanol had m. p. and mixed m. p. 183° and the requisite infrared absorption spectrum.

Dehydrogenation of dihydrorosonolactone (4 g.) with powdered selenium (8 g.) at 320—330° for 36 hr. gave 1 : 7-dimethylphenanthrene (1·6 g.), m. p. and mixed m. p. 85° after purification by chromatography and crystallisation from methanol; the picrate had m. p. and mixed m. p. 132°.

*Dihydrorosonic Acid*.—Formed by warming a mixture of dihydrorosonolactone (0·5 g.) and N-aqueous sodium hydroxide (15 ml.) on the steam-bath for 20 min., a yellow solution remained clear on dilution with water and on acidification gave a precipitate of *dihydrorosonic acid* which was purified from ethyl acetate–light petroleum (b. p. 60—80°) and then methanol, forming prisms (0·3 g.), m. p. 173°, $\lambda_{max.}$ 248 mμ (log ε 4·05), $\lambda_{max.}$ 314 mμ (log ε 1·83), $[\alpha]_D^{18}$ −148° (*c* 2), insoluble in water and readily soluble in cold N-aqueous sodium hydrogen carbonate (Found: C, 75·7; H, 9·47%; equiv., 316, 318. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%; equiv., 318). This acid is inert to the usual carbonyl reagents.

The acid was also formed when a solution of dihydrorosonolactone (1 g.) in alcohol (10 ml.) and 2N-sulphuric acid (10 ml.) was boiled for ½ hr.; the cooled mixture deposited the acid (0·6 g.), m. p. and mixed m. p. 173° (from methanol). On esterification with methyl sulphate–potassium carbonate in boiling acetone (20 ml.) for 6 hr. the acid (0·5 g.) furnished *methyl dihydrorosonate*, b. p. 166°/0·3 mm. (Found: C, 75·8; H, 9·6. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%). Reduction of the ester (1 g.), in methanol (20 ml.), with potassium borohydride (0·45 g.) in water (3 ml., containing 2 drops of N-aqueous sodium hydroxide), added dropwise in 2 hr., gave *γ-lactone* (C) which separated from aqueous methanol in needles (0·4 g.), m. p. 130°, infrared spectrum band at 1786 cm.$^{-1}$ (in $CCl_4$) (Found: C, 79·4; H, 9·9; OMe, 0. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%). This lactone was insoluble in cold 2N-aqueous sodium hydroxide but dissolved when heated under reflux for 1 hr. with N-alcoholic sodium hydroxide. The solution remained clear on dilution with water but addition of excess of 2N-hydrochloric acid precipitated the parent lactone.

Dehydrogenation of dihydrorosonic acid (3·0 g.) with selenium (6·0 g.) by the method employed for dihydrorosololactone gave 1 : 7-dimethylphenanthrene (1·4 g.), m. p. and mixed m. p. 85°, forming the picrate m. p. and mixed m. p. 132°; a phenolic fraction was not obtained.

XUM

*Tetrahydrorosonic Acid.*—On hydrogenation in methanol (80 ml.) with a catalyst (from 0·08 g. of palladium chloride and 0·3 g. of charcoal) dihydrorosonic acid (0·5 g.) slowly absorbed hydrogen (40 ml.) for 6 hr. Purification of the product from methanol gave *tetrahydrorosonic acid* in needles (0·4 g.), m. p. 217°, $[\alpha]_D^{18}$ −11·5 (*c* 1·5) (Found: C, 74·8; H, 10·0%; equiv., 315. $C_{20}H_{32}O_3$ requires C, 75·0; H, 10·1%; equiv., 320). This compound, which is insoluble in water, readily dissolves in N-aqueous sodium hydrogen carbonate and has a negative tetranitromethane reaction in chloroform. The 2 : 4-*dinitrophenylhydrazone* separated from benzene–light petroleum (b. p. 60—80°) in yellow needles, m. p. 259° (Found: C, 62·3; H, 7·5; N, 11·2. $C_{26}H_{36}O_6N_4$ requires C, 62·4; H, 7·2; N, 11·2%), and the *oxime* from aqueous methanol in needles, m. p. 208° (decomp.) (Found: C, 71·5; H, 9·9; N, 4·1. $C_{20}H_{33}O_3N$ requires C, 71·6; H, 9·9; N, 4·2%). Formed quantitatively by the methyl sulphate–potassium carbonate method in 6 hr., *methyl tetrahydrorosonate* separated from light petroleum (b. p. 40—60°) in prisms, m. p. 86° (Found: C, 75·5; H, 10·4; OMe, 9·6. $C_{20}H_{31}O_2{\cdot}OMe$ requires C, 75·4; H, 10·3; OMe, 9·3%), and gave an *oxime* which crystallised from aqueous methanol in needles, m. p. 148° (Found: C, 72·1; H, 10·0; N, 4·0. $C_{21}H_{35}O_3N$ requires C, 72·2; H, 10·1; N, 4·0%).

A mixture of methyl tetrahydrorosonate (0·5 g.), alcohol (5 ml.), and 95% hydrazine hydrate (1·5 ml.) was heated under reflux for 4 hr., cooled, and diluted with water. Purified from aqueous methanol, the precipitate furnished a *substance* in plates (0·25 g.), m. p. 174° (Found: C, 76·2; H, 10·4; N, 9·2; OMe, 0. $C_{20}H_{32}ON_2$ requires C, 75·9; H, 10·2; N, 8·9%). The same product (0·1 g.), m. p. and mixed m. p. 174°, was obtained when a mixture of tetrahydrorosonic acid (1 g.), diethylene glycol (20 ml.), sodium (0·6 g.), and 100% hydrazine hydrate (4 ml.) was heated under reflux at 100° for 1 hr. and then at 200° for 6 hr.

Condensation of methyl tetrahydrorosonate (1 g.) with ethanedithiol (1·5 ml.) was effected by hydrogen chloride at 0° in 1 hr.; 6 hr. later the product was precipitated with methanol and purified from benzene, giving the *mercaptal* in plates (0·93 g.), m. p. 191° (Found: C, 67·3; H, 9·1; OMe, 8·1. $C_{22}H_{38}O_2S_2$ requires C, 67·3; H, 9·3; OMe, 7·6%).

*Methyl Tetrahydrorosolate.*—Reduction of methyl tetrahydrorosonate (0·5 g.) in methanol (5 ml.) was effected with potassium borohydride (0·25 g.) in water (2 ml., containing 2 drops of N-aqueous sodium hydroxide) in 2 hr., and from aqueous methanol the resulting *methyl tetrahydrorosolate* formed needles (0·23 g.), m. p. 157° (Found: C, 74·8; H, 10·8; OMe, 9·4. $C_{20}H_{33}O_3{\cdot}OMe$ requires C, 75·0; H, 10·8; OMe, 9·2%). Prepared with boiling acetic anhydride for 2 hr., the *acetate* formed needles (from aqueous methanol), m. p. 144° (Found: C, 73·1; H, 10·1; OMe, 8·2. $C_{22}H_{35}O_3{\cdot}OMe$ requires C, 73·0; H, 10·1; OMe, 8·2%).

*Dihydrorosenic Acid.*—(*a*) A mixture of dihydrorosololactone (1 g.) and naphthalene-2-sulphonic acid (0·03 g.) (dried over concentrated sulphuric acid) was heated at 3 mm., first with a small flame to initiate effervescence and then on the steam-bath until the mixture became solid (*ca.* 45 min.). An ethereal solution of the product was washed with N-aqueous sodium hydrogen carbonate, and the washings were acidified, giving *dihydrorosenic acid* which separated from light petroleum (b. p. 60—80°) in needles (0·68 g.), m. p. 147°, $[\alpha]_D^{22}$ +205° (*c* 0·1), having an intense orange tetranitromethane reaction in chloroform (Found: C, 79·6; H, 9·7%; equiv., 30·4. $C_{20}H_{30}O_3$ requires C, 79·4; H, 10·0%; equiv., 302).

(*b*) A solution of dihydrorosololactone (0·75 g.) in N-alcoholic hydrochloric acid (75 ml.) was boiled for 2 hr., cooled, diluted with water (50 ml.), basified, and extracted with ether. This extract gave only a small amount of an intractable gum. The residual aqueous liquor was then acidified and extracted with ether, and on evaporation the dried extract left a residue (0·5 g.) which on purification from methanol followed by light petroleum (b. p. 60—80°) furnished dihydrorosenic acid in needles (0·12 g.), m. p. and mixed m. p. 147°. Prepared with diazomethane, *methyl dihydrorosenate* separated from methanol in prisms, m. p. 70° (Found: C, 79·5; H, 9·8; OMe, 9·6. $C_{20}H_{29}O{\cdot}OMe$ requires C, 79·7; H, 10·2; OMe, 9·8%).

Dehydrogenation of dihydrorosenic acid (3 g.) with selenium (6 g.) as previously described gave 1 : 7-dimethylphenanthrene (1·06 g.), m. p. and mixed m. p. 85° (picrate, m. p. and mixed m. p. 135°); a phenolic fraction was not obtained.

*Tetrahydrorosenic Acid.*—Hydrogenation of dihydrorosenic acid (1 g.) in methanol (40 ml.) with a catalyst (from 0·25 g. of palladium chloride and 0·25 g. of charcoal) was complete in 1 hr. (1 mol. absorbed). The resulting *tetrahydrorosenic acid* separated from aqueous methanol in needles, m. p. 151°, $[\alpha]_D^{26}$ −15° (*c* 0·8), having a yellow tetranitromethane reaction in chloroform (Found: C, 79·0; H, 10·4. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

Tetrahydrorosenic acid (25 mg.) was heated in a sealed tube at 250° for 1½ hr., the product

isolated with ether, and the extract washed with N-aqueous sodium hydrogen carbonate, and distilled, to yield a *product* (15 mg.) as a neutral oil, devoid of hydroxyl or carbonyl absorption in the infrared region (Found: C, 87·0; H, 12·4. $C_{19}H_{32}$ requires C, 87·6; H, 12·4%).

*Dihydrorosenol.*—Reduction of methyl dihydrorosenate (2 g.) in ether (80 ml.) with lithium aluminium hydride (0·6 g.) for 48 hr. gave *dihydrorosenol* (1·4 g.), b. p. 160°/0·5 mm., with an orange tetranitromethane reaction in chloroform, $[\alpha]_D^{28}$ +97° (*c* 0·4), $\lambda_{max.}$ 239 mμ (log ε 4·15) (Found: C, 84·2; H, 11·2; OMe, 0. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%). Oxidation of this alcohol (1 g.) in benzene (12 ml.) and *tert.*-butyl alcohol (4 ml.), containing chromic oxide (1 g.), occurred in 8 days. The yellow neutral product furnished *dihydrorosenal semicarbazone* which separated from methanol in needles (0·3 g.), m. p. 218° (Found: C, 73·4; H, 9·5; N, 12·4. $C_{21}H_{33}ON_3$ requires C, 73·4; H, 9·7; N, 12·2%).

*Dehydration of Dihydrorosenol.*—When dihydrorosenol (2 g.) and naphthalene-2-sulphonic acid (0·02 g.) were gradually heated at 0·1 mm. dehydration occurred and an oil distilled at 160°. A solution of the distillate in ether was washed with N-aqueous sodium hydroxide, and water, dried, and distilled, giving a *product* (1 g.), b. p. 152—154°/0·1 mm., $[\alpha]_D^{24}$ −24° (*c* 1·2) (Found: C, 88·7; H, 11·1. $C_{20}H_{30}$ requires C, 88·8; H, 11·2%). Dehydrogenated with powdered selenium (12 g.) at 330—335° for 48 hr., this hydrocarbon (6 g.) gave a product which on purification by chromatography from light petroleum (b. p. 60—80°) on aluminium oxide was obtained as an oil. A solution of this oil in the minimum quantity of alcohol slowly deposited a solid (24 mg.) which on crystallisation from benzene–light petroleum (b. p. 60—80°) gave the anthracene derivative, m. p. and mixed m. p. 240°, described in Part XXXI [1] having the same infrared absorption spectrum.

After the isolation of the crude anthracene derivative the residual methanolic solution was evaporated, leaving an oil (1·2 g.) whose ultraviolet absorption was of the phenanthrene type. After distillation in a vacuum this gave 1 : 7-dimethylphenanthrene picrate which after repeated crystallisation had m. p. and mixed m. p. 128° (85 mg.) and the requisite infrared absorption.

allo- *and* neo-*Hydroxyrosanoic Lactone.*—A solution of tetrahydrorosenic acid (0·28 g.) in sulphuric acid (4 ml.) at −10° was stirred during 45 min., then poured on ice and extracted with ether, and the ethereal solution was washed with N-aqueous sodium hydroxide. There was no acidic fraction. Purification of the neutral fraction from methanol gave *allo*hydroxyrosanoic lactone in prisms (0·1 g.), m. p. 138°, $[\alpha]_D^{20}$ +28·9° (*c* 1 in EtOH) identical with *allo*-hydroxyrosanoic lactone prepared from *iso*(?)ros-11 : 12-en-16-oic acid (preceeding paper) and having the requisite infrared spectrum.

Concentration of the methanolic mother-liquors from the purification of *allo*hydroxyrosanoic lactone furnished a more soluble neutral product, neo*hydroxyrosanoic lactone*, which separated from aqueous methanol in needles (30 mg.), m. p. 123°, $[\alpha]_D^{24}$ −19° (*c* 3·5 in EtOH), having an infrared spectrum identical with that of the second lactone derived from *iso*(?)ros-11 : 12-en-16-oic acid (Found: C, 79·3; H, 10·6. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·6%).

The ultraviolet absorption spectra were determined in 95% EtOH with a Unicam S.P. 500 Spectrophotometer; the infrared spectral data were obtained for $CCl_4$ solutions with a Perkin-Elmer Model 21 Spectrophotometer. [α] refer to $CHCl_3$ solutions unless otherwise stated. The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

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## 371. *The Chemistry of Fungi. Part XXXIII.* The Oxidation of Sclerotioramine and the Structure of Sclerotiorin.*

By H. C. Fielding, Alexander Robertson, R. B. Travers, and W. B. Whalley.

Ozonolysis of *O*-acetylsclerotioramine gives sclerotaminic acid, $C_{13}H_{10}O_6NCl$, which exhibits the properties of a substituted pyridonecarboxylic acid and on reductive aromatisation yields acetic acid together with *apo*sclerotaminic acid (Part XXX [1]). Oxidation of sclerotioramine, and of *apo*sclerotioramine with nitric acid, forms berberonic acid whilst the action of alkaline hydrogen peroxide on tetrahydrosclerotioramine produces (+)-2-(3 : 5-dimethyl-*n*-heptyl)pyridine-4 : 5-dicarboxylic acid.

The structure of sclerotiorin is discussed.

The structure of *apo*sclerotioramine, formed by the reductive aromatisation of sclerotioramine, was discussed in Part XXX [1] and the present communication deals with the oxidation of the parent amine and its derivatives. In the decomposition of the ozonide from *O*-acetylsclerotioramine the alkyl side-chain of the base is removed as 2 : 4-dimethylhexa-2-enal (I; see Chart), the acetoxy-residue is hydrolysed, and there is formed sclerotaminic acid, $C_{13}H_{10}O_6NCl$, which contains a *C*-methyl group, retains the kernel of sclerotioramine and exhibits the pyridone-like properties [1] of its precursor. Thus, on methylation with diazomethane the acid gave methyl *N*-methylsclerotaminate, $C_{13}H_8O_5Cl(NMe)\cdot OMe$, and with methyl iodide–potassium carbonate formed methyl *O*-methylsclerotaminate, $C_{13}H_8O_4NCl(OMe)_2$ and with methyl sulphate–potassium carbonate a mixture of methyl *O*-methyl- and methyl *N*-methyl-sclerotaminate.

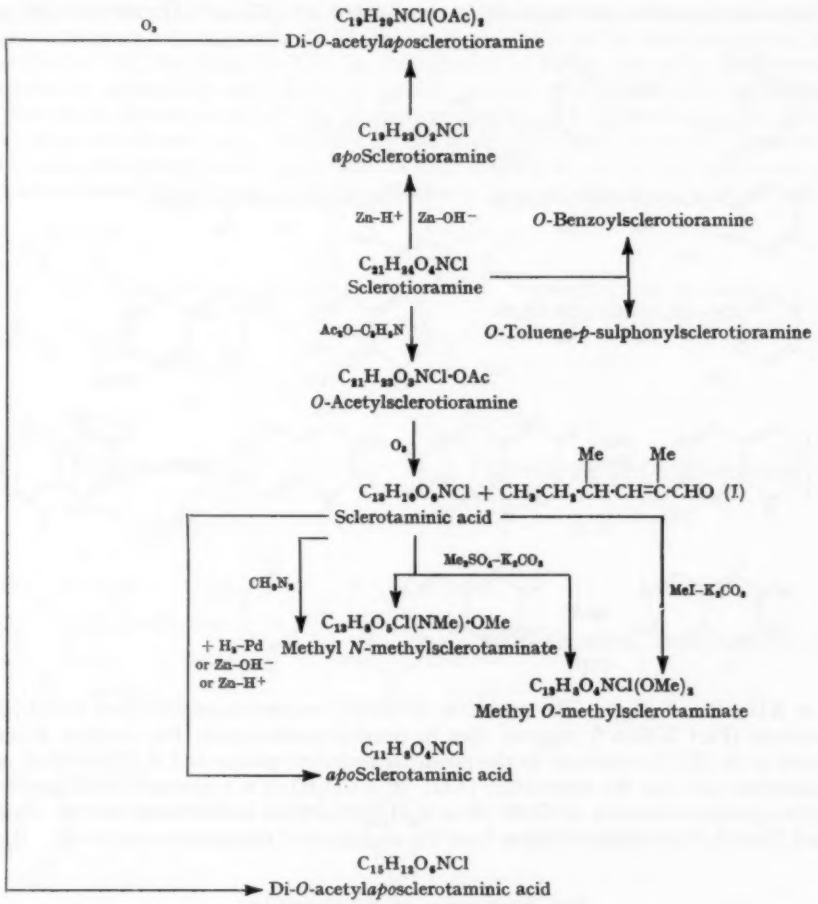
As with the parent sclerotioramine, reductive aromatisation of sclerotaminic acid is effected with hydrogen and a palladium or platinum catalyst in alcohol or acetic acid or with zinc and alkali or with zinc and acid, and is accompanied by simultaneous elimination of two carbon atoms as acetic acid, giving rise to *apo*sclerotaminic acid which is identical with the acid obtained by the ozonolysis of di-*O*-acetyl*apo*sclerotioramine followed by deacetylation of the product; [1] sclerotaminic acid and its derivatives show considerable resistance to oxidation with ozone. The formation of *apo*sclerotaminic acid by the alternative routes proves that the $C_9$ alkyl side-chain does not participate in any of the reactions involved. The interaction of sclerotioramine with benzoyl chloride and toluene-*p*-sulphonyl chloride affords derivatives which, by analogy with the acetate of the base,[1] are formulated as the *O*-benzoate and the *O*-toluene-*p*-sulphonate. On ozonolysis these derivatives give rise to the corresponding *O*-benzoyl-, $C_{20}H_{14}O_7NCl$, and *O*-toluene-*p*-sulphonyl-sclerotaminic acid, $C_{20}H_{16}O_8NClS$, respectively. The foregoing inter-relations are summarised in the Chart.

On oxidation with nitric acid sclerotioramine and its tetrahydro-derivative gave rise to berberonic acid (pyridine-2 : 4 : 5-tricarboxylic acid) (II), and oxidation of tetrahydro*apo*-sclerotioramine with potassium permanganate or alkaline hydrogen peroxide furnished an optically active, dicarboxylic acid, $C_{16}H_{23}O_4N$, which is also formed by the oxidation of tetrahydrosclerotioramine with the same reagents and is characterised as the dimethyl ester. This acid, which has a negative ferrous sulphate reaction in alcohol and thus does not have a carboxyl group in *ortho*-position to the nitrogen atom, gives berberonic acid on oxidation with nitric acid; and, since it exhibits a fluorescein reaction in the usual manner, it is a substituted cinchomeronic acid containing the $C_9$ saturated alkyl side-chain of tetrahydrosclerotioramine and tetrahydro*apo*sclerotioramine which on oxidation provides the 2-carboxyl group of berberonic acid. In agreement with its general properties and

* Part XXXII, preceding paper.

[1] Fielding, Graham, Robertson, Travers, and Whalley, *J.*, 1957, 4931.

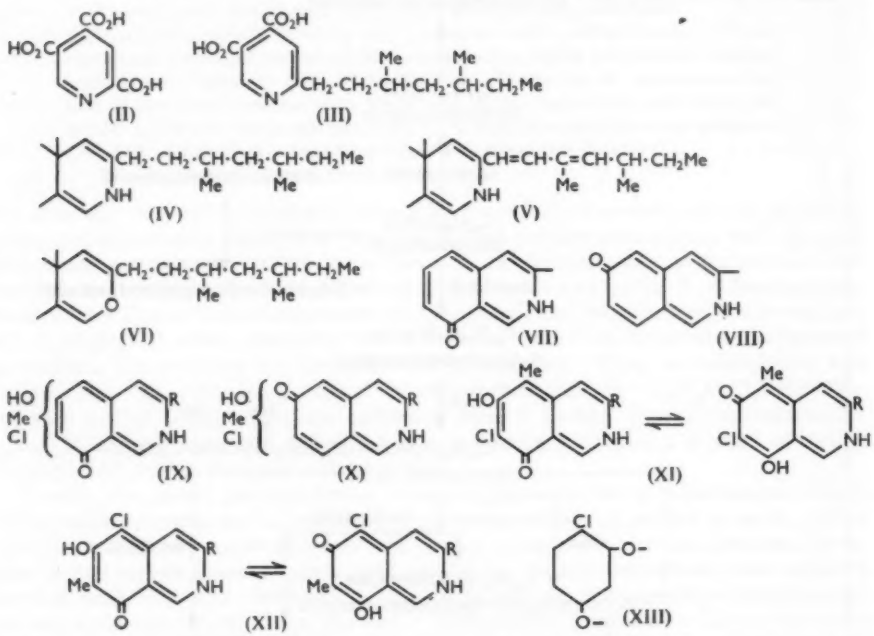
molecular rotation this substituted cinchomeronic acid is clearly (+)-2-(3 : 5-dimethyl-*n*-heptyl)pyridine-4 : 5-dicarboxylic acid (III), and from the comparatively mild conditions employed in its production it is reasonably certain that the residue (IV) obtains in tetrahydrosclerotioramine and hence the system (V) is present in sclerotioramine, a view




compatible with the formation of the amino-compounds from a progenitor of the type (VI) on the assumption that this conversion does not involve a rearrangement (cf. Part XXVIII [3]). Further, the formation of the acid (III) supports conclusively the *iso*quinoline structures proposed in Part XXX [1] for *apo*sclerotaminic acid and its derivatives and, moreover, this heterocyclic kernel cannot be an α-*iso*quinolone but must be an *iso*quinolone of the type (VII) or (VIII), containing a chlorine atom, a hydroxyl group, and a *C*-methyl residue which does not arise in the aromatisation process since, from the Kuhn–Roth estimation, sclerotaminic acid also contains a *C*-methyl group. Hence the formula for *apo*sclerotaminic acid and for *apo*sclerotioramine may be expanded to (IX; R = $CO_2H$) and

[1] Graham, Page, Robertson, Travers, Turner, and Whalley, *J.*, 1957, 4924.
[3] Eade, Page, Robertson, Turner, and Whalley, *J.*, 1957, 4913.

(IX; R = $C_9H_{15}$) or (X; R = $CO_2H$) and (X; R = $C_9H_{15}$) respectively. Since *apo*-sclerotaminic acid and tetrahydro*apo*sclerotioramine do not give a ferric reaction and are not readily oxidised it is reasonably certain that the hydroxyl group and the quinolone-oxygen atom are in the *meta*-position to each other and thus the compounds are resorcinol derivatives and not catechol or quinol derivatives; consequently *apo*sclerotaminic acid and *apo*sclerotioramine are respectively represented by (XI or XII; R = $CO_2H$) and

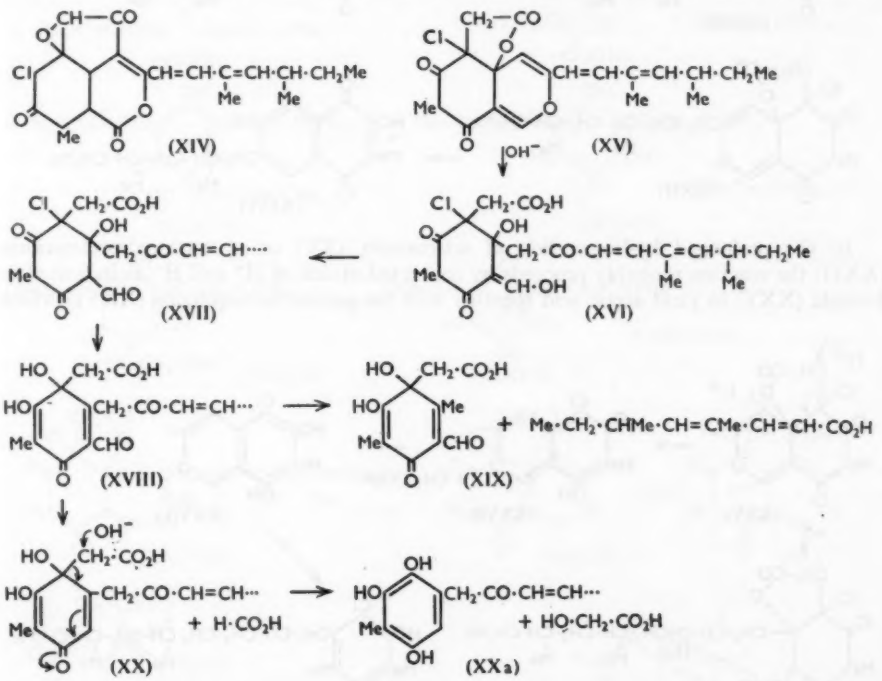



(XI or XII; R = $C_9H_{15}$). The formation of tetrahydrosclerotoquinone from tetrahydrosclerotiorin (Part XXIX [2]) suggests that in tetrahydrosclerotiorin the chlorine atom is situated as in (XIII) relatively to the potential hydroxyl groups and it follows that *apo*-sclerotaminic acid has the orientation (XII; R = $CO_2H$) or a tautomeric modification of it, with *apo*sclerotioramine as (XII; R = $C_9H_{15}$); rational formulations for the various *O*- and *N*-methyl derivatives [1] follow from the structures of the parent compounds.

## The Structure of Sclerotiorin

In view of the exceptionally mild conditions under which this metabolite reacts with ammonia to form the base sclerotioramine [3] it seems reasonable to assume that the replacement of the heterocyclic oxygen atom is not accompanied by an intramolecular rearrangement, a view which is compatible with the infrared data. Further, the ready reductive aromatisation of sclerotioramine and its derivatives to yield the respective *apo*-compounds, together with approximately one molecular proportion of acetic acid, under a wide variety of conditions, affords substantial evidence that a molecular rearrangement does not occur during the aromatisation. On the basis of these assumptions in conjunction with the structures deduced earlier [1-3] for the degradation products of sclerotiorin, the derivation of a complete formulation for sclerotioramine and hence of the parent metabolite implies the insertion into the *apo*sclerotioramine system of a residue $C_2H_2O_2$, in which the ·C·C·O· is intact to account for the production of acetic acid during aromatisation. In this

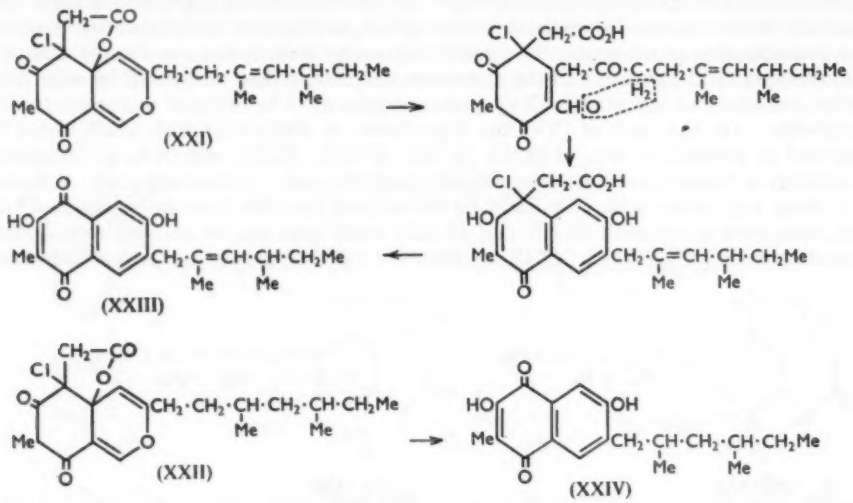
connection it may be noted that the isolation of the oxidation products, the $C_9$-alkylcinchomeronic acid and berberonic acid described in the present work, excludes the type of structure (XIV) proposed provisionally.[4] On the basis of the experimental facts now available there are several ways in which the $C_2H_2O_2$ residue may be inserted (by reversing the aromatisation process) into the *apo*sclerotioramine system so as to comply with the requisite empirical formula. Of the structures which may thus be derived for sclerotioramine and hence for sclerotiorin, (XV) appears at present to be the most acceptable for the metabolite. On the basis of (XV) the degradation of sclerotiorin with alkali would be expected to proceed by way of (XVI), (XVII), XVIII), (XIX), and (XX) (although not necessarily in this sequence) with the ultimate production of 4 : 6-dimethylocta-2 : 4-dienoic acid along with formic acid. Similarly, by the series of reactions previously suggested[2] di- and tetra-hydrosclerotiorin (XXI) and (XXII) could give rise to di- and tetra-hydrosclerotoquinone (XXIII) and (XXIV) respectively together with formic acid accompanied



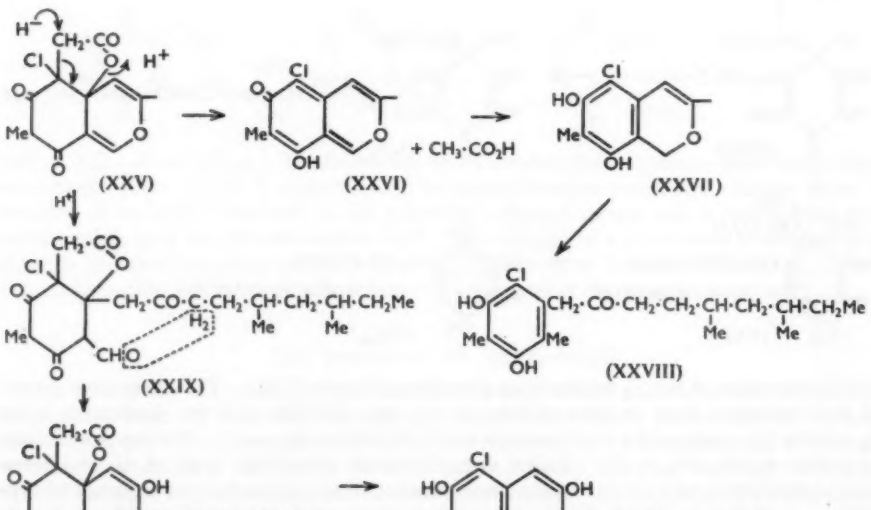

by the extrusion of the $C_2$ fragment as glycollic acid as in (XX). The alternative genesis of these quinones from an intermediate of, *e.g.*, type (XVIII) with the elimination of the $C_2$ residue by a retroaldol condensation would furnish acetic acid. The repeated failure to isolate acetic acid in the alkaline degradation of sclerotiorin (and of di- and tetrahydrosclerotiorin) may be due to the predominance of the aromatisation sequence of type (XX) ⟶ (XXa) in which the $C_2$ fragment is eliminated as glycollic acid, a view in keeping with the failure of β-hydroxy-acids to undergo the retroaldol condensation readily, and with the similar aromatisation of *O*-methylhomofuscin,[5] geodin,[6] and erdin.[6] In connection with the alkaline degradation of sclerotiorin and its derivatives it must be

[4] Powell, Robertson, and Whalley, *Chem. Soc. Special Publ.*, 1956, No. 5, p. 27.
[5] Barton and Hendrickson, *J.*, 1956, 1028.
[6] Calam, Clutterbuck, Oxford, and Raistrick, *Biochem. J.*, 1947, **41**, 458.

noted that the yields of characterisable products are invariably poor and that much intractable resin is produced.



In the prolonged hydrogenation of sclerotiorin (XV) or of tetrahydrosclerotiorin (XXII) the reaction probably proceeds by concerted attack of $H^+$ and $H^-$ as indicated in formula (XXV) to yield acetic acid together with the pyrono-hemiquinone (XXVI) which

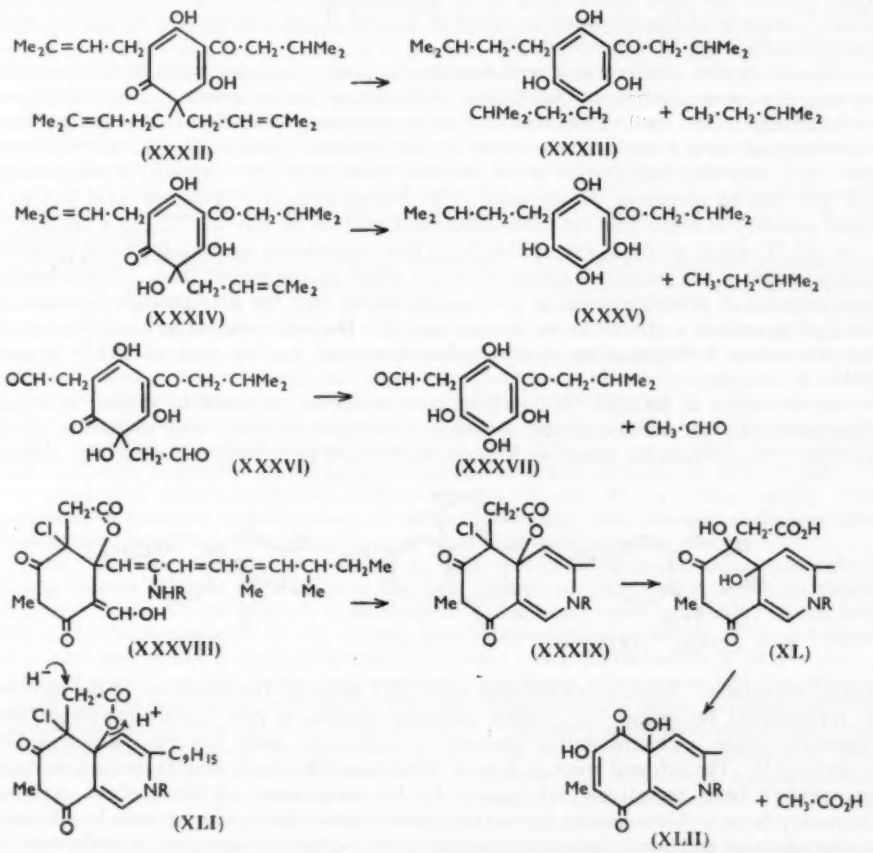


then gives the dihydro-derivative (XXVII) (cf. the hydrogenation of, *e.g.*, citrinin [7]) and ultimately sclerotinol [1] (XXVIII) by fission of the vinyl ether system in (XXVII). The

[7] Brown, Robertson, Whalley, and Cartwright, *J.*, 1949, 867.

acid-catalysed fission of tetrahydrosclerotiorin to an intermediate type (XXIX) and its subsequent cyclisation to (XXX) would account for the production of small quantities of sclerotol (XXXI) in addition to the major product, sclerotinol, when acetic acid is employed as the solvent for exhaustive hydrogenation.

This aromatisation of sclerotiorin with simultaneous extrusion of acetic acid has a close parallel in the behaviour of numerous morphine derivatives with acetic anhydride, *e.g.*, thebaine is thus aromatised to acetylthebaol with the extrusion of the *N*-methylethylamine residue as 2-acetoxyethyl-*N*-acetylmethylamine. This and the closely associated reactions in the morphine series have been interpreted by Stork [8] as proceeding



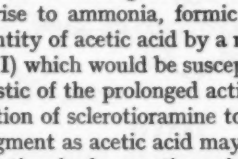

by synchronous attack of acetate anions and acetyl cations. Even closer analogies to the sclerotiorin series are provided by the reductive aromatisation of various natural and synthetic *gem*-substituted derivatives of phloroglucinol: thus aromatisation of lupulone (XXXII) by hydrogenation with a palladium catalyst at room temperature proceeds readily with extrusion of *iso*pentane [9,10] and the formation of the phloroglucinol (XXXIII), whilst humulone (XXXIV) furnishes the tetrahydric phenol (XXXV) and *iso*pentane.[9,10]

[8] Stork, in Manske and Holmes, "The Alkaloids," Academic Press, New York, 1952, p. 175.
[9] Riedl, *Chem. Ber.*, 1952, **85**, 692.
[10] Wieland, *Ber.*, 1925, **58**, 102, 2012.

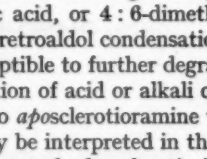
On the other hand reduction of lupulone (XXXII) with a platinum catalyst saturates the double bonds in the *iso*pentene side-chains and aromatisation does not occur in the absence of activation provided by the allyl system. The activation provided by the carbonyl of the $\cdot CH_2 \cdot CO \cdot$ system in schlerotiorin is not readily suppressed by hydrogenation and thus the extrusion of acetic acid occurs as readily with a platinum as with a palladium catalyst. Further, the allylic-lactone character of sclerotiorin will facilitate hydrogenolysis. Further analogies to the behaviour of sclerotiorin are provided in the aromatisation of (XXXVI) to (XXXVII) by zinc and very dilute acid [11] and of 4-dichloromethyl-4-methyl*cyclo*hexa-2 : 5-dienone with zinc and acetic acid to *p*-cresol and methylene chloride.[12] The aromatisation of lupulone and related compounds has recently been interpreted by Riedl and Nickl [13] in terms of the synchronous attack of $H^+$ and $H^-$ as suggested in the present work to explain the behaviour of sclerotiorin.

The interaction of sclerotiorin with ammonia or primary amines seems likely to proceed by way of an open-chain form (XXXVIII) of the formyl ketone system in sclerotiorin, and to be similar to the ready formation of 4-methoxycarbonyl-7-methyl-1-*iso*quinolone from 4-methoxycarbonyl-7-methyl*iso*coumarin or the hydrated open-chain acid derived from it.[14] It is clear that degradation of the resulting bases (XXXIX) with acid or alkali would not give rise to ammonia, formic acid, or 4 : 6-dimethylocta-2 : 4-dienoic acid but to a small quantity of acetic acid by a retroaldol condensation by way of (XL) to a product of type (XLII) which would be susceptible to further degradation to the intractable products characteristic of the prolonged action of acid or alkali on the parent base. The reductive aromatisation of sclerotioramine to *apo*sclerotioramine with the simultaneous extrusion of the $C_2$ fragment as acetic acid may be interpreted in the same manner as the first stage of the exhaustive hydrogenation of tetrahydrosclerotiorin, *i.e.*, by way of (XLI) to give (XII; $R = C_9H_{15}$).

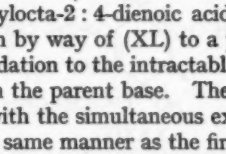
On the basis of formula (XV), sclerotiorin would be expected to exhibit reactions associated with the α-chloro-ketone system, *e.g.*, halogen exchange with sodium iodide in acetone. The metabolite, however, is moderately stable to prolonged heating with sodium




(XLIII)




(XLIV)




(XLV)

iodide in acetone. Steric considerations could be a factor in the resistance of the chlorine to replacement by iodine; *e.g.*, whilst phenacyl chloride is very rapidly converted into phenacyl iodide, α-chloro*iso*butyrophenone is extremely inert towards sodium iodide in acetone.[15] The infrared spectral data of tetrahydrosclerotiorin and its derivatives have previously [1] been tentatively interpreted by the assignment of the highest carbonyl frequency to an α-chloro-ketone, but on the present views this band must now be allocated to the γ-lactone and hence the carbonyl group of the α-chloro-ketone appears as the band of an isolated carbonyl group (1705—1709 cm.$^{-1}$). Investigations concerning the spectra of α-halogeno-ketones [16,17] have demonstrated that isolated-carbonyl frequency is observed if the chromophores are approximately at right angles.

The structure (XV) now suggested for sclerotiorin may be considered as arising

[11] Howard and Tatchall, *J.*, 1954, 2400.
[12] Auwers and Keil, *Ber.*, 1902, **35**, 4207.
[13] Riedl and Nickl, *Chem. Ber.*, 1956, **89**, 1838.
[14] Ungnade, Nightingale, and French, *J. Org. Chem.*, 1945, **10**, 533.
[15] Reeve, McCaffery, and Kaiser, *J. Amer. Chem. Soc.*, 1954, **78**, 2281.
[16] Jones, Ramsey, Herling, and Dobriner, *ibid.*, 1952, **74**, 2828.
[17] Bellamy, Thomas, and Williams, *J.*, 1956, 3704.

biogenetically from the addition of the elements of acetic acid to a fundamental quinone-like compound (XXVI), the reactivity of which would follow from the well-established behaviour of quinones in forming 2 : 3-adducts. On this basis alternative structures, *e.g.*, (XLIII), (XLIV), or (XLV), may be derived but as these are in one way or another incompatible with the present experimental findings they need not be further considered at present.

## Experimental

*Sclerotaminic Acid.*—A stream of ozone and oxygen was passed into a solution of *O*-acetylsclerotioramine (2 g.) in ethyl acetate (20 ml.) at room temperature until the deep red solution became pale yellow (*ca.* 2 hr.). Decomposition of the ozonide with water (50 ml.) for 12 hr. yielded a red solid which on purification from aqueous methanol furnished *sclerotaminic acid* in scarlet needles or plates (0·8 g.), m. p. 201° (Found: C, 47·4; H, 3·6; N, 4·3; Cl, 11·2; *C*-Me, 5·4. $C_{13}H_{10}O_6NCl,H_2O$ requires C, 47·4; H, 3·8; N, 4·3; Cl, 10·8; *C*-Me, 5·0%). This acid is readily soluble in 2N-aqueous sodium hydrogen carbonate with effervescence, and gives an intense purple colour with ferrous sulphate in alcohol and a violet colour with copper sulphate.

Distillation of the aqueous liquors left on isolation of the solid gave (+)-α-methylbutyraldehyde, isolated and characterised as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 128°. When the time of ozonolysis was reduced to 1 hr. 2 : 4-dimethylhexa-2-enaldehyde was isolated and characterised as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 158°.

Treatment of sclerotaminic acid (0·5 g.) in methanol (10 ml.) with an excess of diazomethane for 15 min. gave *methyl N-methylsclerotaminate* which separated from aqueous methanol in brick-red needles (0·2 g.), m. p. 76° (Found: C, 52·6; H, 4·1; N, 4·2; OMe, 8·2. $C_{13}H_8O_5ClNMe{\cdot}OMe$ requires C, 53·0; H, 4·1; N, 4·1; OMe, 9·1%). This ester, which is insoluble in 2N-aqueous sodium hydrogen carbonate and has a negative ferrous sulphate reaction in alcohol, was recovered unchanged after treatment with methyl sulphate– or methyl iodide–potassium carbonate in boiling acetone for 2 hr. Methylation of sclerotaminic acid (0·5 g.) by methyl iodide–potassium carbonate in boiling acetone (25 ml.) for 1½ hr. gave *methyl O-methylsclerotaminate* which formed brick-red needles (0·25 g.), m. p. 108°, from aqueous methanol, with a negative ferrous sulphate reaction in alcohol [Found: C, 53·2; H, 4·0; N, 4·0; OMe, 17·0. $C_{13}H_8O_4NCl(OMe)_2$ requires C, 53·0; H, 4·1; N, 4·1; OMe, 18·3%]. This compound is insoluble in 2N-aqueous sodium carbonate and was recovered unchanged after having been heated with methyl sulphate–potassium carbonate in boiling acetone.

Methylation of sclerotaminic acid (0·5 g.) with methyl sulphate–potassium carbonate in boiling acetone (25 ml.) for 4 hr. gave a mixed product, m. p. 95—100°, which by chromatography from ether–benzene (2 : 1) on neutralised aluminium oxide followed by elution with the same solvent was resolved into methyl *O*-methylsclerotaminate (0·2 g.), m. p. and mixed m. p. 108°, and methyl *N*-methylsclerotaminate (0·05 g.), m. p. and mixed m. p. 76°.

A stream of ozone and oxygen was passed into a solution of sclerotaminic acid (1 g.) in ethyl acetate (50 ml.) at room temperature for 3 hr. and the solvent evaporated, leaving a colourless glass which was decomposed with water (50 ml.). Next day the red solid was purified from aqueous methanol, yielding unchanged starting material (0·6 g.), m. p. and mixed m. p. 200°. The residual aqueous liquors did not give a precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate. Ozonolysis for much longer periods gave the same result. Under similar conditions methyl *N*-methylsclerotaminate was not attacked by ozone.

*Di-O-acetylaposclerotaminic Acid.*—(*a*) A solution of sclerotaminic acid (1 g.) in acetic acid (100 ml.) containing palladium–charcoal (from 1 g. of charcoal and 0·25 g. of palladium chloride) was shaken in hydrogen until absorption ceased (about 1 mol.) and the initially red solution became yellow. Evaporation of the filtered solution followed by purification of the residue from methanol gave *aposclerotaminic acid* in pale yellow needles (0·45 g.), m. p. >300° (Found: C, 48·4; H, 4·5; N, 5·1; *C*-Me, 4·5. $C_{11}H_8O_4NCl,H_2O$ requires C, 48·6; H, 3·7; N, 5·2; 1*C*-Me, 5·5%). On acetylation this compound gave di-*O*-acetyl*apo*sclerotaminic acid,[1] m. p. and mixed m. p. 233° (Found: C, 53·3; H, 3·5; N, 4·0. Calc. for $C_{15}H_{12}O_6NCl$: C, 53·4; H, 3·6; N, 4·2%), which with methanolic diazomethane furnished methyl di-*O*-acetyl*apo*sclerotaminate in needles, m. p. 184°, identical (mixed m. p. and infrared absorption spectrum) with a specimen obtained from di-*O*-acetyl*apo*sclerotioramine [1] (Found: C, 54·5; H, 4·2; N, 3·9. Calc. for



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$C_{16}H_{14}O_6NCl$: C, 54·6; H, 4·0; N, 4·0%). When this hydrogenation was effected in alcohol (100 ml.) the yield of the same product was (0·6 g.).

(*b*) A solution of sclerotaminic acid (2 g.) in 2N-aqueous sodium hydroxide (20 ml.) was shaken with zinc dust (2 g.) until the deep red solution became yellow (*ca.* 15 min.). The mixture was filtered into an excess of 2N-sulphuric acid at 0° and the precipitate purified from methanol or dioxan, giving *apo*sclerotaminic acid in pale yellow needles (1·2 g.), m. p. >300° (Found: C, 48·7; H, 3·8; N, 5·0. Calc. for $C_{11}H_8O_4NCl,H_2O$: C, 48·6; H, 3·7; N, 5·2%). The di-*O*-acetate had m. p. and mixed m. p. 235° (Found: C, 53·3; H, 3·7; N, 4·2. Calc. for $C_{15}H_{12}O_6NCl$: C, 53·4; H, 3·6; N, 4·2%). Sclerotaminic acid (2 g.), which had been distilled with water under reduced pressure to remove traces of volatile acidic material, until the distillate was neutral, and which had a negative acetyl value, was degraded with zinc and alkali, and the acidic aqueous liquors remaining after the isolation of the crude *apo*sclerotaminic acid were distilled (with the addition of water as required) until all the volatile acid was removed. After being neutralised (phenolphthalein) with aqueous sodium hydroxide the distillate was evaporated and the sodium salts treated with *o*-phenylenediamine in the usual manner, yielding 2-methylbenziminazole, m. p. and mixed m. p. 176°.

(*c*) A solution of sclerotaminic acid (0·5 g.) in alcohol (50 ml.) containing platinic oxide (50 mg.) was shaken in hydrogen for 2 hr. Absorption of gas then ceased and the pale yellow solution deposited crystals. The warmed solution was filtered and the solvent evaporated, giving *apo*sclerotaminic acid which separated from alcohol in green-yellow needles (0·3 g.), m. p. >320°, and was identified by conversion into the diacetate, m. p. and mixed m. p. 235°.

*Methylation of* apo*Sclerotaminic Acid.*—Methylation of this acid (0·5 g.), suspended in ether, with diazomethane furnished *methyl* NO-*dimethyl*apo*sclerotaminate* which separated from dioxan in needles, m. p. 130°, insoluble in cold 2N-aqueous sodium hydrogen carbonate [Found: C, 56·4; H, 4·3; N, 5·0. $C_{11}H_8O_2Cl(NMe)(OMe)_2$ requires C, 56·9; H, 4·8; N, 4·7%].

Methylation of methyl *apo*sclerotaminate (0·6 g.) by methyl iodide–potassium carbonate in boiling acetone (30 ml.) for 3 hr. gave methyl di-*O*-methyl*apo*sclerotaminate which separated from aqueous acetone in needles (0·4 g.), m. p. 168°, identical (m. p., mixed m. p., and infrared spectrum) with the compound from di-*O*-acetyl*apo*sclerotioramine (Part XXX [1]) [Found: C, 57·0; H, 4·9; N, 5·3; OMe, 30·7. Calc. for $C_{11}H_5ONCl(OMe)_3$: C, 56·9; H, 4·8; N, 4·7; OMe, 31·5%]. The residue left on evaporation of the mother-liquors from the purification of methyl di-*O*-methyl*apo*sclerotaminate was chromatographed from benzene on activated aluminium oxide. Elution of a red band with the same solvent yielded an amorphous product. Subsequently a yellow band was eluted with methanol which provided a yellow solid and on crystallisation from the same solvent this gave methyl *NO*-dimethyl*apo*sclerotaminate in yellow needles, m. p. and mixed m. p. 224° [Found: C, 56·8; H, 4·5; N, 4·7; OMe, 21·5. Calc. for $C_{12}H_8O_2NCl(OMe)_2$: C, 56·9; H, 4·8; N, 4·7; OMe, 21·0%].

The same products were obtained in like proportion by methylation of *apo*sclerotaminic acid with methyl iodide– or methyl sulphate–potassium carbonate.

Hydrolysis of the di-*O*-methyl ester (1 g.) with boiling 2N-aqueous sodium hydroxide (25 ml.) for 1 hr. furnished *di*-O-*methyl*apo*sclerotaminic acid*, forming needles (0·7 g.), m. p. 227°, from methanol [Found: C, 55·5; H, 4·6; N, 4·7; OMe, 20·2; Cl, 12·0. $C_{11}H_6O_2NCl(OMe)_3$ requires C, 55·4; H, 4·3; N, 4·9; OMe, 22·0; Cl, 12·6%] which regenerated the ester with methyl iodide–potassium carbonate. Hydrolysis of the ester (0·2 g.) with boiling concentrated hydrochloric acid (15 ml.) for 3 hr. also gave di-*O*-methyl*apo*sclerotaminic acid (0·15 g.), m. p. and mixed m. p. 227°.

On being boiled with hydrobromic acid (2 ml.; *d* 1·49) for 4 hr. methyl di-*O*-methyl*apo*sclerotaminate (0·2 g.) gave *apo*sclerotaminic acid, m. p. >300°, identified by conversion into the di-*O*-acetate, m. p. and mixed m. p. 235°.

*Chlorination of Methyl* apo*Sclerotaminate.*—A solution of this ester (0·2 g.) in phosphorus oxychloride (5 ml.) was heated at 130° for 1 hr., and the cooled mixture poured on ice and neutralised with sodium hydrogen carbonate. Purification of the precipitate from dioxan gave a *chloro-derivative* (0·09 g.) of the ester, m. p. 175° in needles (Found: C, 49·5; H, 3·5; Cl, 19·8. $C_{12}H_8O_2NCl_2$ requires C, 50·4; H, 3·2; Cl, 24·8%).

O-*Toluene*-p-*sulphonate of Sclerotioramine.*—A solution of toluene-*p*-sulphonyl chloride (2 g.) in pyridine (10 ml.) was added to sclerotioramine (2 g.), dissolved in pyridine (20 ml.) at 0°, and after having been kept at 0° for 1 hr. and then at room temperature for 4 hr. the solution was again cooled to 0° and more toluene-*p*-sulphonyl chloride (2 g.) added; 24 hr. later the red

mixture was poured on ice, the product isolated with ether, and the ethereal solution washed successively with ice-cold 2N-aqueous sodium hydroxide, water, 2N-hydrochloric acid, and water. Evaporation of the dried solution left a syrup which crystallised from methanol, giving the O-*toluene*-p-*sulphonate* of sclerotioramine in yellow needles (2·1 g.), m. p. 154° (Found: C, 61·5; H, 5·6; N, 2·6; Cl, 7·2. $C_{28}H_{30}O_6NClS$ requires C, 61·7; H, 5·5; N, 2·6; Cl, 6·4%). On being warmed with concentrated ammonia or hydrochloric acid this ester slowly regenerated sclerotioramine.

A stream of ozone and oxygen was passed through a solution of the foregoing ester (0·2 g.) in ethyl acetate (25 ml.) for 15 min., and on evaporation of the solvent in a vacuum the residual ozonide was decomposed with water (25 ml.) for 12 hr., giving a colourless solid which on purification from methanol furnished the O-*toluene*-p-*sulphonate* of sclerotaminic acid in needles (0·08 g.), m. p. 174° (decomp.), soluble in cold 2N-aqueous sodium hydrogen carbonate and having a negative ferric chloride and ferrous sulphate reaction in alcohol (Found: C, 54·8; H, 3·3; N, 3·3; Cl, 9·1. $C_{20}H_{16}O_8NClS$ requires C, 51·6; H, 3·5; N, 3·0; Cl, 7·7%). Formed with diazomethane, the *methyl ester* separated from methanol in yellow needles, m. p. 146° (Found: C, 52·6; H, 3·7; Cl, 8·1. $C_{21}H_{18}O_8NClS$ requires C, 52·6; H, 3·8; Cl, 7·4%).

The aqueous liquors from the ozonolysis furnished (+)-α-methylbutyraldehyde, characterised as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 128°.

O-*Benzoylsclerotioramine*.—Sclerotioramine (2 g.), dissolved in pyridine (25 ml.), was treated at 0° with a solution of benzoyl chloride (1 ml.) in pyridine (5 ml.) and 3 hr. later the mixture was poured on ice and extracted with ether. The ethereal extract was successively washed with 2N-aqueous sodium hydroxide, water, 2N-hydrochloric acid, and water, dried, and evaporated, leaving a residue which on crystallisation from methanol gave O-*benzoylsclerotioramine* in yellow needles (1·5 g.), m. p. 186° (Found: C, 68·3; H, 5·7; N, 2·8. $C_{28}H_{29}O_8NCl$ requires C, 68·0; H, 5·7; N, 2·8%). Ozonolysis of this benzoate (0·5 g.) in ethyl acetate (25 ml.) at room temperature for ½ hr. followed by decomposition of the ozonide in the usual manner furnished O-*benzoylsclerotaminic acid* in needles (0·1 g.), m. p. 152° from methanol (Found: C, 57·4; H, 3·2; N, 3·6. $C_{30}H_{14}O_7NCl$ requires C, 57·8; H, 3·4; N, 3·4%).

*Oxidation of Sclerotioramine*.—(*a*) Concentrated nitric acid (*d* 1·52; 20 ml.) and water (1·5 ml.) were added (with cooling) to sclerotioramine (5 g.) and next day the mixture was heated on the steam-bath for 26 hr. with addition of more nitric acid (15 ml.) and water (1 ml.) after 6 hr. and 14 hr. respectively. The pale yellow solution was evaporated on the steam-bath to remove traces of nitric acid, and the residue treated with water (50 ml.) and again evaporated. A solution of this solid in water (50 ml.) was extracted with ether, treated with charcoal at 100°, filtered, concentrated, and kept. Berberonic acid (pyridine-2 : 4 : 5-tricarboxylic acid) then slowly separated in needles (1·2 g.), m. p. and mixed m. p. 245° (decomp.) (after drying) with rapid heating, having an infrared absorption spectrum identical with that of an authentic specimen prepared by the oxidation of berberine sulphate with nitric acid (Found: C, 45·4; H, 2·6; N, 6·7; O, 44·7; Cl, 0. Calc. for $C_9H_5O_6N$: C, 45·5; H, 2·4; N, 6·6; O, 45·5%).

Oxidation of tetrahydrosclerotioramine (1 g.) with nitric acid under similar conditions furnished berberonic acid (0·1 g.), m. p. and mixed m. p. 245° (decomp.), and having the requisite infrared absorption spectrum.

(*b*) A solution of potassium permanganate (1·5 g.) in water (30 ml.) was added gradually to sclerotioramine (2 g.) dissolved in 0·5N-aqueous sodium hydroxide (100 ml.) at 10°. The solution was cleared with sulphur dioxide, filtered, and extracted with ether to furnish (+)-α-methylbutyraldehyde, identified as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 132°. A solution of potassium permanganate (4 g.) in water (80 ml.) was added gradually to the residual aqueous solution at 80° and, when colourless, the filtered solution was acidified with hydrochloric acid and evaporated to dryness in a vacuum and a solution of the residual solid in water (30 ml.) extracted with ether; then the aqueous solution was evaporated to dryness and the residue extracted with hot alcohol (2 × 10 ml.). Evaporation of the alcohol furnished a sticky solid which was purified from hot water, to give berberonic acid (0·1 g.), m. p. and mixed m. p. 245° (decomp.), further identified by the infrared spectrum (Found: C, 46·2; H, 2·6; N, 6·6; O, 45·3; Cl, 0. Calc. for $C_9H_5O_6N$: C, 45·5; H, 2·4; N, 6·6; O, 45·5%).

The oxidation of *apo*sclerotaminic acid (1·5 g.) with potassium permanganate (3·5 g.) by the method used for the oxidation of sclerotioramine gave berberonic acid (90 mg.), m. p. and mixed m. p. 245° (decomp.).

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*Oxidation of Tetrahydroaposclerotioramine.*—(*a*) A solution of potassium permanganate (1·5 g.) in water (30 ml.) was added gradually in 30 min. to tetrahydro*apo*sclerotioramine (1 g.) in 0·5N-aqueous sodium hydroxide (20 ml.) and the reaction completed by warming the mixture to 70°. The cooled mixture was filtered, acidified with 2N-hydrochloric acid, and extracted with ether, and the extract washed with 2N-aqueous sodium hydrogen carbonate. The ether solution then contained a negligible quantity of product but acidification of the bicarbonate extract yielded a precipitate of 2-(3 : 5-*dimethyl*-n-*heptyl*)*pyridine*-4 : 5-*dicarboxylic acid* which on purification from benzene–alcohol or aqueous acetone formed needles (0·2 g.), m. p. 194°, readily soluble in 2N-aqueous sodium hydrogen carbonate, having a negative ferric chloride and ferrous sulphate reaction in alcohol but giving an intense fluorescein reaction (Found: C, 65·6; H, 7·7; N, 4·9; O, 19·6; Cl, 0. $C_{16}H_{23}O_4N$ requires C, 65·5; H, 7·9; N, 4·8; O, 21·0%), $[\alpha]_D^{20}$ +12° (*c* 10·18 in EtOH), $[M]_D^{20}$ +3396°.

(*b*) Hydrogen peroxide (2 ml. of 100-vol.) at 0° was added to a solution of tetrahydro*apo*-sclerotioramine (0·6 g.) in N-aqueous sodium hydroxide (10 ml.), and the mixture was kept at this temperature for 18 hr., then gently warmed until effervescence began, cooled, acidified with 2N-hydrochloric acid, and extracted with ether. Evaporation of the dried extract furnished 2-(3 : 5-dimethyl-*n*-heptyl)pyridine-4 : 5-dicarboxylic acid (0·13 g.), m. p. and mixed m. p. 194° after purification, which had an infrared absorption spectrum identical with that of the specimen prepared as by (*a*) (Found: C, 65·0; H, 7·8; N, 4·7%).

*Oxidation of Tetrahydrosclerotioramine.*—Prepared at 0°, a mixture of hydrogen peroxide (3 ml. of 100-vol.) and tetrahydrosclerotioramine (1 g.) in 2N-aqueous sodium hydroxide (20 ml.) was kept at 0° for 20 hr. with the addition of more peroxide (3 ml. of 100-vol.) after 2 hr., acidified, and extracted with ether. Evaporation of the dried extract left 2-(3 : 5-dimethyl-*n*-heptyl)pyridine-4 : 5-dicarboxylic acid, forming needles (0·2 g.), m. p. and mixed m. p. 194°, from aqueous acetone (Found: C, 65·8; H, 7·8; N, 5·1. Calc. for $C_{16}H_{23}O_4N$: C, 65·6; H, 7·9; N, 4·8%). Esterification of this acid (0·8 g.) with ethereal diazomethane (20 ml.) at 0° furnished *dimethyl* 2-(3 : 5-*dimethyl*-n-*heptyl*)*pyridine*-4 : 5-*dicarboxylate* as a pale yellow oil (0·5 g.), b. p. 170°/0·75 mm., insoluble in 2N-aqueous sodium hydrogen carbonate [Found: C, 67·2; H, 8·5; N, 4·6; OMe, 18·3. $C_{14}H_{21}O_2N(OMe)_2$ requires C, 67·3; H, 8·5; N, 4·4; OMe, 19·3%].

Oxidation of 2-(3 : 5-dimethyl-*n*-heptyl)pyridine-4 : 5-dicarboxylic acid (0·5 g.) with nitric acid by the method described previously gave berberonic acid (0·05 g.), m. p. and mixed m. p. 245° (decomp.), having the requisite infrared absorption spectrum.

*Degradation of Sclerotiorin with Acid.*—A suspension of sclerotiorin (10 g.) in 10N-sulphuric acid (250 ml.) was heated under reflux for 32 hr. by which time most of the sclerotiorin had dissolved. The cooled, diluted mixture was filtered and distilled with the addition of distilled water to maintain the volume of reaction liquid. The acid distillate was neutralised (phenolphthalein) with N-aqueous sodium hydroxide and evaporated, and the sodium salts (2 g.) were converted into methylbenziminazole (150 mg.), m. p. and mixed m. p. 174°. The mixed m. p. with benziminazole was *ca.* 148°.

*Exhaustive Hydrogenation of Sclerotiorin in Alcohol.*—A solution of sclerotiorin (5 g.) in sodium-treated alcohol (250 ml.) containing platinic oxide (50 mg.) was shaken in hydrogen until approximately 6 mols. of hydrogen had been absorbed (*ca.* 3 hr.). The colourless filtrate was saturated with ammonia, then the alcohol was removed under reduced pressure and the residue extracted with hot distilled water (20 ml.). Evaporation of the aqueous solution gave a colourless, crystalline residue (3 g.) which by interaction with *o*-phenylenediamine in the usual manner gave 2-methylbenziminazole (0·1 g.), m. p. and mixed m. p. 174° (mixed m. p. with benziminazole, *ca.* 154°). A control experiment under the same conditions gave no inorganic salts.

The ultraviolet absorption spectra were measured in 95% alcohol with a Unicam S.P. 500 Spectrophotometer, and the infrared spectral data were obtained in Nujol on a Grubb-Parsons S.3 double-beam spectrophotometer. The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

UNIVERSITY OF LIVERPOOL. [*Received, November 14th*, 1957.]

# 372. *The Chemistry of Fungi. Part XXXIV.* Rotiorin, a Metabolite of* Penicillium sclerotiorum *van Beyma.*

By G. B. Jackman, Alexander Robertson, R. B. Travers, and W. B. Whalley.

The new pigment, rotiorin, $C_{23}H_{24}O_5$ or less probably $C_{22}H_{22}O_5$, from *P. sclerotiorum*, is similar in many respects to sclerotiorin. On alkaline degradation rotiorin furnishes 4 : 6-dimethylocta-2 : 4-dienoic acid, and with ammonia gives rotioramine, $C_{23}H_{25}O_4N$, which is readily aromatised to an extended *iso*quinolone and on oxidation yields 2-(3 : 5-dimethyl-*n*-heptyl)-pyridine-4 : 5-dicarboxylic acid.

The structure of rotiorin is discussed.

The present paper describes preliminary studies of a new pigment, rotiorin, isolated [1,2] from the mycelium of *Penicillium sclerotiorum* van Beyma, the methods being similar to those employed for sclerotiorin.[2,3,4] Rotiorin, which is optically active and has the molecular formula $C_{23}H_{24}O_5$ or $C_{22}H_{22}O_5$, is devoid of methoxyl and hydroxyl groups, but, from the infrared absorption spectrum, appears to contain several carbonyl residues. From the results of numerous analyses of the compound and its derivatives the formula, $C_{23}H_{24}O_5$, appears the more likely and, although absolute distinction is not yet possible this will be used in the present communication. The pigment is not reduced by sulphur dioxide or sodium dithionite in aqueous dioxan and, although reaction occurred with hydroxylamine, semicarbazide, and phenylhydrazine, crystalline derivatives could not be isolated.

Rotiorin is extremely sensitive to alkali and on degradation with sodium hydroxide solution gave 4 : 6-dimethylocta-2 : 4-dienoic acid (I) and 2 : 4-dimethylhex-2-enal [2] (II); degradation with sodium hydrogen carbonate solution afforded, in addition to the dienoic acid, small amounts of acetaldehyde. Despite repeated attempts it has not been possible to isolate a crystalline product from the hydrogenation or the acetylation of rotiorin. On ozonolysis rotiorin gave (+)-α-methylbutyraldehyde; no other product could be isolated. Repeated attempts to obtain a ketone, analogous to pentanorsclerotiorone,[2] by oxidation with chromic acid or by ozonolysis were unsuccessful.

Like its congener, sclerotiorin, rotiorin reacts rapidly with ammonia to form rotioramine, $C_{23}H_{25}O_4N$, which on ozonolysis gives the aldehyde (II) but on degradation with alkali does not furnish the dienoic acid (I), acetaldehyde, or ammonia. Further, on oxidation with nitric acid, rotioramine, like sclerotioramine, furnishes berberonic acid (III; R = $CO_2H$), showing that the base contains the system (IV). With methylamine rotiorin yields *N*-methylrotioramine, $C_{24}H_{27}O_4N$, in low yield, which is also obtained in even smaller amounts by the *N*-methylation of rotioramine. Rotioramine is readily aromatised with zinc and alkali or with zinc and acetic acid (cf. the behaviour of sclerotioramine [4]) to give *apo*rotioramine, $C_{22}H_{27}O_2N$, which is readily soluble in aqueous sodium hydroxide solution, furnishes an unstable monohydrochloride and a monoacetyl derivative, $C_{24}H_{29}O_3N$, and exhibits the properties of an *iso*quinoline. From the infrared spectrum (1745 cm.$^{-1}$, aromatic acetate) together with the decrease in m. p. observed in passing from *apo*rotioramine to the acetate it is clear that this derivative is an *O*-acetate. The presence of an isolated carbonyl residue in *apo*rotioramine is shown by the infrared absorption at 1698 cm.$^{-1}$, in conjunction with the formation of a 2 : 4-dinitrophenylhydrazone (isolated as the hydrochloride), $C_{28}H_{31}O_5N_5$,HCl, $\lambda_{max.}$ 360 mμ (log ε, 4·43). Similarly, the hydrochloride of the mono-*O*-acetate exhibits aromatic acetate (1758 cm.$^{-1}$) and isolated carbonyl

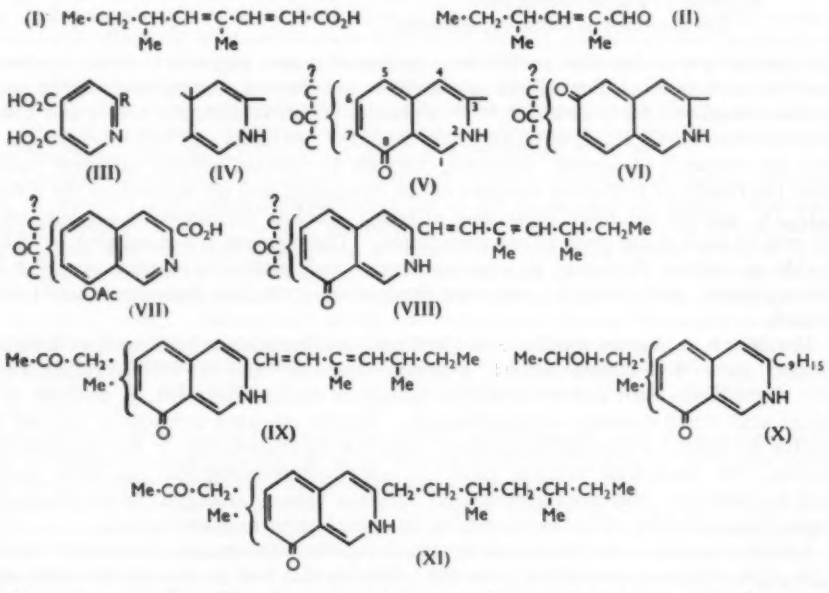
* Part XXXIII, preceding paper.

[1] Powell, Robertson, and Whalley, *Chem. Soc. Special Publ.*, 1956, No. 5, p. 27.
[2] Eade, Page, Robertson, Turner, and Whalley, *J.*, 1957, 4913.
[3] Graham, Page, Robertson, Travers, Turner, and Whalley, *J.*, 1957, 4924.
[4] Fielding, Graham, Robertson, Travers, and Whalley, *J.*, 1957, 4931.

XUM

(1699 cm.$^{-1}$) absorption in the infrared spectrum. Volatile acids are not produced during the aromatisation of rotioramine to *apo*rotioramine.

Methylation of *apo*rotioramine with methyl sulphate and alkali furnishes *N*-methyl-*apo*rotioramine, which is devoid of hydroxyl and methoxyl groups, is rather unstable, and is identical with *N*-methyl*apo*rotioramine obtained from the aromatisation of *N*-methylrotioramine. The formation of this derivative, which is insoluble in alkali and exhibits infrared absorption at 1725 cm.$^{-1}$ (unconjugated carbonyl) and at 1623 cm.$^{-1}$ ($\alpha\beta\alpha'\beta'$-unsaturated carbonyl), in conjunction with the solubility of *apo*rotioramine in aqueous alkali and the oxidation of rotioramine to berberonic acid indicates the presence of an extended *iso*quinolone residue (V) or (VI) in *apo*rotioramine.




Ozonolysis of *O*-acetyl*apo*rotioramine gives *O*-acetyl*apo*rotaminic acid, $C_{16}H_{15}O_4N$, of type (VII), the positive ferrous sulphate reaction of which indicates that the carboxyl group and hence the original $C_9H_{15}$ residue, is situated in the *ortho*-position to the nitrogen atom, as in sclerotioramine.[4] Consequently the structure for *apo*rotioramine may be expanded to (VIII). Since *O*-acetyl*apo*rotaminic acid contains three *C*-methyl residues and furnishes an almost quantitative yield of iodoform, the partial structure (VIII) for *apo*rotioramine may be further expanded to (IX) in which the molecular formula allows the isolated carbonyl group to be separated from the aromatic nucleus by only one carbon atom. Further, *apo*rotioramine does not readily yield an anhydro-compound devoid of the isolated carbonyl residue (*i.e.*, a 2-methylfuran derivative) and hence the quinolone-oxygen atom and the $CH_3{\cdot}CO{\cdot}CH_2{\cdot}$ residue are not likely to be in the *ortho*-position to each other.[5]

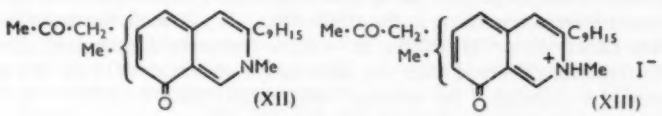
Ozonolysis of *O*-benzoyl*apo*rotioramine yields *O*-benzoyl*apo*rotaminic acid which, as expected, appears to contain two *C*-methyl residues.

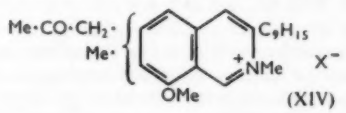
Reduction of the isolated carbonyl residue of *apo*rotioramine with potassium borohydride gives the secondary alcohol, *apo*rotioraminol (X) (infrared absorption at 3250 cm.$^{-1}$). On ozonolysis its di-*O*-acetate yields di-*O*-acetylrotaminolic acid which in agreement with previous considerations contains four *C*-methyl residues.

[5] Whalley and Lloyd, *J.*, 1956, 3213.

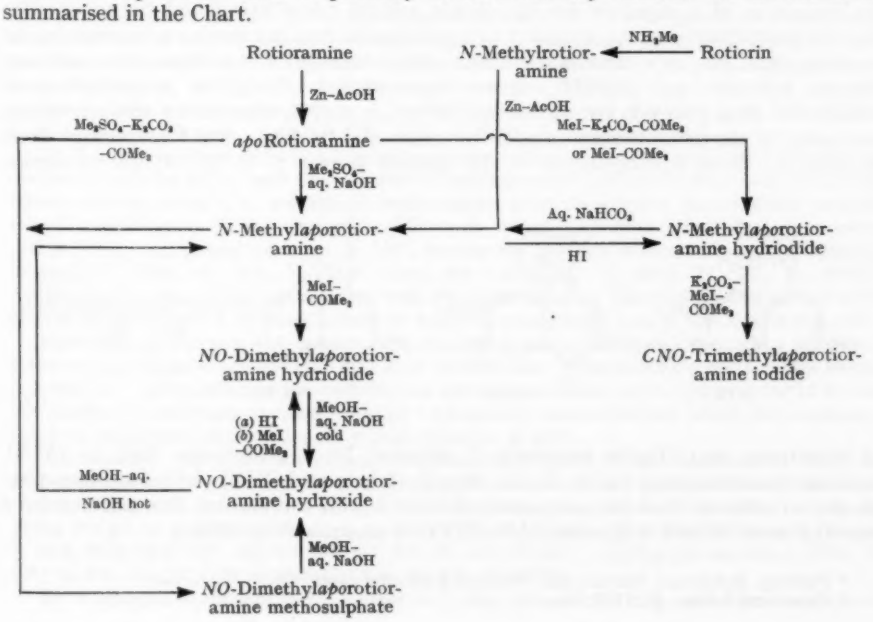
Hydrogenation of rotioramine to tetrahydrorotioramine has not been achieved, but reduction of *O*-acetyl*apo*rotioramine furnishes *O*-acetyltetrahydro*apo*rotioramine, characterised as the hydrochloride, $C_{24}H_{34}O_3NCl$, whilst *apo*rotioramine gives tetrahydro*apo*rotioramine $C_{23}H_{33}O_2N$ (XI) which is oxidised by potassium permanganate to the cinchomeronic acid [6] (III; R = $CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2Me$).

The action of methylating agents on *apo*rotioramine is complex but in agreement with the established behaviour of *iso*quinolones. Thus whilst methyl sulphate and alkali yield *N*-methyl*apo*rotioramine (XII), methyl iodide in acetone gives *N*-methyl*apo*rotioramine hydriodide (XIII) which readily yields the free base (XII) with sodium hydrogen carbonate.



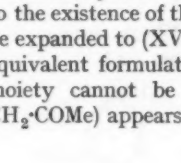




Methylation of either *apo*rotioramine or *N*-methyl*apo*rotioramine with methyl sulphate–potassium carbonate in acetone furnished *NO*-dimethyl*apo*rotioramine methosulphate (XIV; X = $MeSO_4$). With cold alkali this gave the unstable, insoluble base (XIV; X = OH) which was converted by hydriodic acid into the salt (XIV; X = I) and by warm alkali into *N*-methyl*apo*rotioramine. The same iodide (XIV; X = I) has been formed from *N*-methyl*apo*rotioramine by direct addition of methyl iodide to the quinonoid system. The action of methyl iodide–potassium carbonate–acetone on *apo*rotioramine, *N*-methyl-*apo*rotioramine hydriodide (XIII), or *NO*-dimethyl*apo*rotioramine iodide (XIV; X = I) furnished a product which is probably a *CNO*-trimethyl iodide. These results are summarised in the Chart.

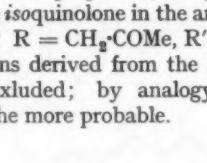



XUM

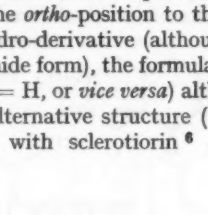
*The Structure of Rotiorin.*—The experimental evidence indicates that *apo*rotioramine has the molecular formula, $C_{22}H_{27}O_2N$, and an extended *iso*quinolone structure containing one *C*-methyl and an acetonyl group as substituents. The isolation of 2-(3 : 5-dimethyl-*n*-heptyl)pyridine-4 : 5-dicarboxylic acid from the potassium permanganate oxidation of tetrahydro*apo*rotioramine confirms the presence of an *iso*quinolone system which must be of type (V) or (VI) and is devoid of substituents in the 1- and the 4-position. Analogy with sclerotiorin [6] suggests that the nuclear *C*-methyl residue occupies the 7-position of the *iso*quinolone residue as in (XV). In addition, since *apo*rotioramine does not appear to have the *iso*quinolone-oxygem atom in the *ortho*-position to the acetonyl residue, as is indicated by our failure to prepare an anhydro-derivative (although this may be ascribed to the existence of the *iso*quinolone in the amide form), the formula for *apo*rotioramine may be expanded to (XVI; R = $CH_2$·COMe, R′ = H, or *vice versa*) although at this stage other equivalent formulations derived from the alternative structure (VI) for the *iso*quinolone moiety cannot be exluded; by analogy with sclerotiorin [6] (XVI; R = H, R′ = $CH_2$·COMe) appears the more probable.



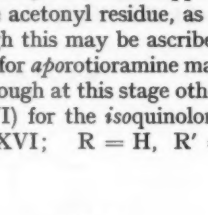
(XV)



(XVI)

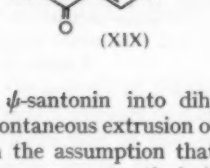


(XVII)

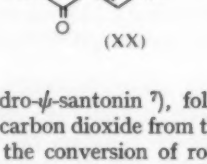


(XVIII)

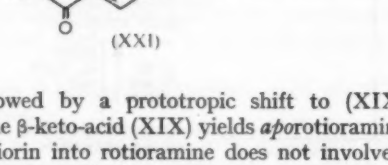
On the basis of the $C_{23}$ formula for rotiorin the conversion of rotioramine into *apo*-rotioramine involves the addition of two hydrogen atoms and the elimination of two oxygen atoms and one carbon atom (which is not extruded as formic acid). These considerations and the foregoing experimental facts in conjunction with the arguments advanced during the derivation of a structure for the closely related sclerotiorin,[6] and the assumption that the aromatisation of rotioramine to *apo*rotioramine does not involve an intramolecular rearrangement, may be rationalised in terms of structure (XVII) for rotioramine, although obvious variants, *e.g.*, (XVIII), cannot be excluded. Reductive aromatisation of rotioramine then proceeds by way of (XIX) which may be formed by the mechanism envisaged for the aromatisation of sclerotioramine and its derivatives,[6] or perhaps more probably by direct hydrogenolysis of the diallylic lactone to (XX) (cf. the conversion



(XIX)



(XX)



(XXI)

of ψ-santonin into dihydro-ψ-santonin [7]), followed by a prototropic shift to (XIX). Spontaneous extrusion of carbon dioxide from the β-keto-acid (XIX) yields *apo*rotioramine. On the assumption that the conversion of rotiorin into rotioramine does not involve a rearrangement rotiorin is represented by (XXI) or an equivalent variant.

[6] Fielding, Robertson, Travers, and Whalley, preceding paper.
[7] Clemo and Cocker, *J.*, 1946, 30.

## Experimental

*Rotiorin.*—Only comparatively small amounts of rotiorin were obtained when *Penicillium sclerotiorum* van Beyma was cultivated for the production of sclerotiorin on a Czapek–Dox type of medium. A somewhat improved yield resulted when the mould was grown on a Raulin–Thom medium containing glucose (6·0 g., all amounts per l.), ammonium tartrate (2·6 g.), tartaric acid (2·6 g.), ammonium phosphate (0·4 g.), potassium carbonate (0·4 g.), magnesium carbonate (0·26 g.), ammonium sulphate (0·17 g.), zinc sulphate (0·05 g.), and ferrous sulphate (0·05 g.) at 25° for 14—17 days, in penicillin flasks each containing 500 ml. of medium. The thick orange-red mycelial felts were collected, dried at room temperatue for 7 days, milled, and percolated with ether for 24 hr. Evaporation of this extract followed by purification from methanol furnished sclerotiorin, m. p. 206—207°. Subsequent exhaustive percolation of the mycelium with more ether gave rotiorin which was purified by repeated recrystallisation from alcohol, forming long red needles, m. p. 246° (decomp.), which sublimed unchanged at 190°/0·005 mm. and had a negative ferric reaction, $[\alpha]_D^{22}$ +5,080° (*c* 0·002 in $CHCl_3$), $\nu_{max.}$ 1745, 1660, 1640, 1620 cm.$^{-1}$, and $\lambda_{max.}$ 238, 242, 282, 312, and 493 mμ (log ε 5·71, 5·71, 5·65, and 5·91 respectively) (Found: C, 72·4, 72·0, 72·0; H, 6·3, 6·9, 6·4; O, 21·2, 21·4. Calc. for $C_{22}H_{22}O_5$: C, 72·1; H, 6·0; O, 21·9. Calc. for $C_{23}H_{24}O_5$: C, 72·6; H, 6·3; O, 21·1%). This pigment is sparingly soluble in the usual organic solvents and insoluble in 2N-aqueous sodium carbonate or hydroxide but readily dissolves in aqueous-alcoholic sodium hydroxide, giving a deep-red solution. The compound is not extracted from ethereal solution by aqueous sodium hydroxide. 1000 Flasks furnished *ca.* 8 kg. of dried mycelium from which sclerotiorin (300—350 g.) and rotiorin (100—150 g.) were extracted; the yield of rotiorin varied from one batch to another for no apparent reason.

*Degradation of Rotiorin with Alkali.*—(*a*) A mixture of rotiorin (1 g.) and 2N-aqueous sodium hydroxide (60 ml.) was slowly distilled during 2½ hr., in nitrogen, and the volume of the reaction mixture maintained by the addition of distilled water (200 ml.) as required. The pigment rapidly formed a red solution which later deposited a black solid, leaving a supernatant orange liquor which was decanted, acidified with 2N-sulphuric acid, filtered, and distilled, giving 4 : 6-dimethylocta-2 : 4-dienoic acid (10 mg.), m. p. and mixed m. p. 92°, $[\alpha]_D^{19}$ +67·6° (*c* 2 in EtOH), which was isolated from the distillate with ether (Found: C, 71·6; H, 9·6. Calc. for $C_{10}H_{16}O_2$: C, 71·4; H, 9·5%). With an excess of aqueous 2 : 4-dinitrophenylhydrazine sulphate this distillate furnished the 2 : 4-dinitrophenylhydrazone of 2 : 4-dimethylhexa-2-enal which separated from alcohol in orange needles (60 mg.), m. p. and mixed m. p. 158°, identical with a specimen from sclerotiorin [2] (Found: C, 55·0; H, 6·1; N, 18·4. Calc. for $C_{14}H_{18}O_4N_4$: C, 54·9; H, 5·9; N, 18·3%). In another experiment this aldehyde was isolated as the semicarbazone from light petroleum (b. p. 60—80°) in plates, m. p. and mixed m. p. 148° (Found: C, 59·3; H, 9·2; N, 23·1. Calc. for $C_9H_{17}ON_3$: C, 59·0; H, 9·3; N, 22·9%).

(*b*) A mixture of rotiorin (1 g.) and N-aqueous sodium hydrogen carbonate (60 ml.) was distilled slowly for 2½ hr. with the addition of distilled water (200 ml.) to maintain the volume. Mixed with an excess of 2 : 4-dinitrophenylhydrazine sulphate solution, the distillate furnished the 2 : 4-dinitrophenylhydrazone of acetaldehyde which separated from alcohol in yellow plates (0·1 g.), m. p. and mixed m. p. 163°, having the requisite infrared absorption spectrum (Found: C, 43·5; H, 3·6; N, 24·6. Calc. for $C_8H_8O_4N_4$: C, 42·9; H, 3·6; N, 25·0%). Acidification of the cooled hydrolysate with 2N-sulphuric acid, followed by distillation of the filtered solution, gave 4 : 6-dimethylocta-2 : 4-dienoic acid (0·15 g.), m. p. and mixed m. p. 92°.

*Ozonolysis of Rotiorin.*—A stream of ozone and oxygen was passed through a solution of rotiorin (1 g.) in ethyl acetate (150 ml.) at 0° for 135 min. The originally red solution became pale yellow. After isolation the ozonide was decomposed with water (250 ml.) for 12 hr. and the clarified hydrolysate distilled, yielding (+)-α-methylbutyraldehyde which was isolated as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 133°.

*Rotioramine.*—(*a*) A mixture of aqueous ammonia (*d* 0·88; 25 ml.) and rotiorin (5 g.) was shaken gently for 15 min., and the resulting purple solution poured into an excess of 2N-hydrochloric acid at 0°. Purified from alcohol, the precipitate gave *rotioramine* in violet, rectangular, plates (3·5 g.), m. p. 261° (decomp.), $\nu_{max.}$ 1730, 1710, 1640, 1605, 1590, 3200, 3025 cm.$^{-1}$ (Found: C, 72·6, 72·6, 72·6, 72·7; H, 6·3, 6·5, 6·7, 6·7; N, 3·7, 3·7, 3·7. $C_{22}H_{23}O_4N$ requires C, 72·3; H, 6·3; N, 3·8. $C_{23}H_{25}O_4N$ requires C, 72·8; H, 6·6; N, 3·7%).

(*b*) A solution of rotiorin (1 g.) in ether (3 l.) was shaken for 1 min. with aqueous ammonia

XUM

(*d* 0·88; 5 ml.); the ammoniacal liquor was separated from the ethereal solution which was washed with water, followed by dilute hydrochloric acid, and evaporated to about 500 ml. On being kept this gave rotioramine (0·8 g.), m. p. and mixed m. p. 261° (decomp.). Rotioramine is insoluble in 2N-aqueous sodium hydroxide but readily dissolves in 2N-aqueous sodium hydroxide containing 1% of alcohol, to form a solution which remains clear on dilution with water.

N-*Methylrotioramine*.—A solution of rotiorin (0·3 g.) in ether (1 l.) was shaken with aqueous methylamine (from 2 ml. of base and 20 ml. of water) for 1 hr. and the aqueous layer acidified with dilute hydrochloric acid. The ethereal solution was separated, washed, and evaporated, leaving N-*methylrotioramine*, which crystallised from alcohol in prisms (30 mg.), m. p. 226° (decomp.) (Found: C, 74·0; H, 7·7. $C_{24}H_{27}O_4N$ requires C, 73·3; H, 6·9. $C_{23}H_{25}O_4N$ requires C, 72·8; H, 6·6%). Attempts to prepare this compound by the methylation of rotioramine under a variety of conditions were unsuccessful although occasionally traces of the *N*-methyl derivative were obtained.

*Oxidation of Rotioramine*.—Concentrated nitric acid (6 ml.) was diluted with water (1 ml.) and added to rotioramine (2 g.). Next day the resulting red solution was heated on the steam-bath for 21 hr.; more concentrated nitric acid (10 ml.) and water (1 ml.) were added after 7 and after 14 hr. The mixture was then diluted with water, evaporated to small volume, and again diluted and evaporated. This was repeated until all the nitric acid had been removed. The residual solution was then cooled, extracted with ether, treated with charcoal, and concentrated, to give berberonic acid, m. p. and mixed m. p. 238° (decomp.), having the requisite infrared absorption spectrum.

apo*Rotioramine*.—A mixture of rotioramine (2 g.), zinc dust (2 g.), and acetic acid (20 ml.) was heated under reflux in nitrogen for 15 min. and the orange solution cooled, diluted with ether (50 ml.), and filtered into a saturated solution of sodium hydrogen carbonate (500 ml.). The liquor was extracted with ether, and the combined extracts were washed, dried, and evaporated to *ca.* 20 ml. apo*Rotioramine* then separated in cream-coloured needles (1·2 g.) and on purification from alcohol had m. p. 186°, a negative ferric reaction in alcohol, and $[\alpha]_D^{22}$ +57° (*c* 0·2 in $CHCl_3$) [Found: C, 78·0, 78·0, 78·6, 78·6; H, 8·0, 8·0, 8·1, 8·0; N, 3·9, 4·0, 4·0%; *M* (Rast), 304. $C_{22}H_{27}O_2N$ requires C, 78·3; H, 8·0; N, 4·2%; *M*, 337. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·8; N, 4·3%; *M*, 323]. *apo*Rotioramine is unchanged on sublimation *in vacuo* and readily dissolves in 2N-aqueous sodium hydroxide from which it is precipitated unchanged by carbon dioxide. The solution in aqueous methanol containing hydrochloric acid deposits bright yellow needles of an unstable hydrochloride, m. p. 230°, which on crystallisation from aqueous alcohol regenerates *apo*rotioramine. Formed with alcoholic–acidic 2 : 4-dinitrophenylhydrazine, the 2 : 4-*dinitrophenylhydrazone* of *apo*rotioramine hydrochloride separated from alcohol in yellow needles, m. p. 252° (decomp.) (Found: C, 60·8; H, 5·9; N, 12·1. $C_{28}H_{31}O_5N_5,HCl$ requires C, 60·7; H, 5·6; N, 12·6. $C_{27}H_{29}O_8N_5,HCl$ requires C, 60·1; H, 5·6; N, 13·0%). Pyridine–acetic anhydride at room temperature for 12 hr. gave a quantitative yield of O-*acetyl*apo*rotioramine*, plates, m. p. 86° [from light petroleum (b. p. 40—60°)] (Found: C, 75·7, 75·3; H, 7·6, 7·8; N, 3·5, 3·7. $C_{24}H_{29}O_3N$ requires C, 76·0; H, 7·7; N, 3·7. $C_{23}H_{27}O_3N$ requires C, 75·6; H, 7·5; N, 3·8%). This acetate is readily deacetylated with 2N-aqueous sodium hydroxide to the parent base. Addition of 2N-hydrochloric acid to this acetate in alcohol furnished the *hydrochloride* in green needles, m. p. 166° (Found: C, 66·6, 66·3; H, 7·5, 7·4; N, 3·3. $C_{23}H_{27}O_3N,HCl,H_2O$ requires C, 65·9; H, 7·1; N, 3·3. $C_{24}H_{29}O_3N,HCl,H_2O$ requires C, 66·5; H, 7·4; N, 3·2%. Found in specimen dried at 80°: C, 68·3; H, 7·0. $C_{24}H_{29}O_3N,HCl$ requires C, 69·4; H, 7·2%). With pyridine–benzoyl chloride, *apo*rotioramine (1·5 g.) furnished O-*benzoyl*apo*rotioramine*, pale yellow needles (1·0 g.), m. p. 148° (from methanol) (Found: C, 79·1; H, 6·8; N, 2·5. $C_{29}H_{31}O_3N$ requires C, 79·0; H, 7·0; N, 3·1%).

*Reduction of* apo*Rotioramine*.—Potassium borohydride (0·5 g.) in water (10 ml.) was added during 1 hr. to *apo*rotioramine (0·5 g.) suspended in alcohol (15 ml.) and distilled water (5 ml.). The base rapidly dissolved and was then gradually replaced by a white precipitate. Next day the mixture was added to an excess of dilute hydrochloric acid, and the resulting green unstable hydrochloride isolated and decomposed with 2N-aqueous sodium hydrogen carbonate to give apo*rotioraminol* which separated from alcohol in plates (0·4 g.), m. p. 240° (Found: C, 77·6; H, 8·8. $C_{22}H_{29}O_2N$ requires C, 77·9; H, 8·6. $C_{21}H_{27}O_2N$ requires C, 77·5; H, 8·4%). The *hydrochloride* separated from aqueous alcohol in pale yellow needles, m. p. 224° (Found:

C, 70·1; H, 8·3. $C_{22}H_{29}O_2N$,HCl requires C, 70·3; H, 8·0%). Prepared from *apo*rotioraminol (1 g.) by pyridine–acetic anhydride di-*O*-acetyl*apo*rotioraminol (1 g.) was obtained as an oil which furnished quantitatively a *hydrochloride* in yellow needles, m. p. 105° (from ethanol) (Found: C, 67·8; H, 7·6. $C_{26}H_{33}O_4N$,HCl requires C, 67·9; H, 7·4. $C_{25}H_{31}O_4N$,HCl requires C, 67·4; H, 7·2%).

*Di*-O-*acetyl*a*porotaminolic Acid.*—A mixture of oxygen and ozone was passed through a solution of di-*O*-acetyl*apo*rotioraminol (0·5 g.) in ethyl acetate (50 ml.) for 20 min. Removal of the solvent furnished the ozonide as a colourless gum which was decomposed with water (10 ml.) during 12 hr. Purification of the resultant product from ethanol gave *di*-O-*acetyl*a*porotaminolic acid* in needles (0·1 g.), m. p. 196° (Found: C, 62·3; H, 5·7; *C*-Me, 16·4. $C_{18}H_{19}O_6N$ requires C, 63·6; H, 5·6; 4*C*-Me, 17·4. $C_{17}H_{17}O_6N$ requires C, 61·6; H, 5·2; 4*C*-Me, 18·1%). This acid has a negative reaction with ferric chloride but exhibits a bright orange colour with ferrous sulphate in alcohol.

*Ozonolysis of* O-*Acetyl*a*porotioramine.*—A slow stream of ozone and oxygen was passed through a solution of *O*-acetyl*apo*rotioramine (1 g.) in ethyl acetate (25 ml.) at room temperature for 40 min. Removal of the solvent in a vacuum followed by decomposition of the ozonide with water (20 ml.) for 12 hr. furnished a pale yellow solid which was purified from methanol, giving O-*acetyl*a*porotaminic acid* in needles (0·25 g.), m. p. 240° (decomp.), with a negative ferric reaction and absorption at 1754 (aromatic acetate) and at 1724 cm.$^{-1}$ (isolated carbonyl) (Found: C, 63·0, 63·4, 63·4; H, 5·1, 4·9, 5·2; N, 4·2, 4·2. $C_{15}H_{13}O_5N$ requires C, 62·7; H, 4·6; N, 4·9. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0; N, 4·7%). This acid, which is insoluble in 2N-aqueous sodium carbonate but readily soluble in cold 2N-aqueous sodium hydroxide, gives a bright orange colour with ferrous sulphate and is unchanged by acetylating reagents. When a suspension of *O*-acetyl*apo*rotaminic acid (0·1 g.) in alcohol (50 ml.) was saturated with hydrogen chloride and heated under reflux for 3 hr., evaporation of the clear yellow solution gave a yellow solid which was purified by ethanol, to yield a*porotaminic acid hydrochloride* (0·05 g.) in yellow needles, m. p. 265° (Found: C, 56·9; H, 4·7. $C_{14}H_{13}O_4N$,HCl requires C, 56·8; H, 4·7%).

*Ozonolysis of* O-*Benzoyl*a*porotioramine.*—A stream of ozonised oxygen was passed through a solution of *O*-benzoyl*apo*rotioramine (0·75 g.) in ethyl acetate (20 ml.) at room temperature, until the solution was colourless (*ca.* 45 min.). Removal of the solvent under reduced pressure followed by decomposition of the ozonide with water (10 ml.) during 12 hr. furnished a solid which was purified from methanol, to yield O-*benzoyl*a*porotaminic acid* in prisms (0·08 g.), m. p. 280—285° (decomp.) (Found: C, 66·5; H, 5·0; *C*-Me, 7·3. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7. $C_{21}H_{17}O_5N,H_2O$ requires C, 66·1; H, 5·0; 2*C*-Me, 7·8%).

*Hydrogenation of* O-*Acetyl*a*porotioramine and of* apo*Rotioramine.*—A solution of this acetate (1 g.) in alcohol (50 ml.) containing palladium–charcoal (from 1 g. of charcoal and 0·15 g. of palladium chloride) was shaken in hydrogen until 2·5 mol. had been absorbed. Evaporation of the filtered solution gave a glass but treatment in alcohol with 2N-hydrochloric acid furnished O-*acetyltetrahydro*a*porotioramine hydrochloride* which separated from acetone in almost colourless needles (0·6 g.), m. p. 130° (Found: C, 68·6; H, 7·9. $C_{24}H_{33}O_3N$,HCl requires C, 68·7; H, 8·1. $C_{22}H_{31}O_5N$,HCl requires C, 68·1; H, 8·0%).

When a solution of *apo*rotioramine (0·5 g.) in ethyl acetate (100 ml.) containing the same catalyst was shaken in hydrogen the absorption of *ca.* 2½ mol. of gas occurred in 2½ hr., giving a colourless solution which contained an amorphous product. This was converted into *tetrahydro*a*porotioramine hydrochloride* which separated from ethyl acetate in yellow plates (0·3 g.), m. p. 150° (Found: C, 70·1, 69·8; H, 8·3, 8·5; N, 3·4. $C_{22}H_{31}O_2N$,HCl requires C, 70·0; H, 8·5; N, 3·7. $C_{21}H_{29}O_2N$,HCl requires C, 69·5; H, 8·2; N, 3·9%).

*Oxidation of* O-*Acetyltetrahydro*a*porotioramine Hydrochloride.*—A suspension of this hydrochloride (1 g.) in 2N-aqueous sodium hydroxide (20 ml.) was warmed until complete dissolution occurred (5 min.). A solution of potassium permanganate (3 g.) in water (75 ml.) was added gradually, initially at room temperature and then finally at 70° to complete the oxidation. The warm mixture was filtered, the cooled, acidified filtrate extracted with ether (2 × 150 ml.), and the extract dried and evaporated, to yield a product which on purification from aqueous acetone gave 2-(3 : 5-dimethyl-*n*-heptyl)pyridine-4 : 5-dicarboxylic acid in needles (0·04 g.), m. p. and mixed m. p. 195°.

*Methylation of* apo*Rotioramine.*—(*a*) A solution of the compound (1 g.) in acetone (30 ml.) containing methyl iodide (3 ml.) was heated under reflux for 4 hr., and the crystalline precipitate

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was collected and purified from methanol, giving the *hydriodide* of *N*-methyl*apo*rotioramine in yellow needles (0·8 g.), m. p. 252° (decomp.) (Found: C, 57·2, 57·6, 57·2; H, 6·1, 6·2, 6·3; N, 2·8; OMe, 0. $C_{23}H_{29}O_3N$,HI requires C, 57·4; H, 6·3; N, 2·9. $C_{22}H_{27}O_2N$,HI requires C, 56·8; H, 5·8; N, 3·0%). Trituration of this salt (1 g.) with aqueous sodium hydrogen carbonate gave *N-methylaporotioramine* which was purified from benzene, forming unstable red needles (0·5 g.), m. p. 196° (decomp.) (Found: C, 74·5, 73·7; H, 8·4, 8·2; N, 3·6; NMe, 5·4; OMe, 0. $C_{23}H_{29}O_2N$,$H_2O$ requires C, 74·8; H, 8·4; N, 3·9. $C_{22}H_{27}O_2N$,$H_2O$ requires C, 74·4; H, 8·2%). The same product, m. p. and mixed m. p. 196°, was obtained in poor yield by treating *apo*rotioramine with methyl sulphate and aqueous sodium hydroxide at room temperature or *N*-methylrotioramine with zinc and alkali under the conditions employed for the preparation of *apo*rotioramine.

(*b*) When a solution of *N*-methyl*apo*rotioramine (0·6 g.) and methyl iodide (3 ml.) in acetone (15 ml.) was heated under reflux for 1 hr., purification of the crystalline precipitate gave NO-*dimethylaporotioramine iodide* which separated from methanol in yellow needles (0·4 g.), m. p. 216°, containing ionisable iodine (Found: C, 58·1; H, 6·8; N, 2·8; OMe, 6·5; NMe, 5·4. $C_{24}H_{32}O_3NI$ requires C, 58·4; H, 6·5; N, 2·8; OMe, 6·3; NMe, 5·9. $C_{23}H_{30}O_3NI$ requires C, 57·6; H, 6·3; N, 3·0; OMe, 6·5; NMe, 6·1%). Treatment of this salt (1 g.) in methanol with excess of 2N-aqueous sodium hydroxide gave an orange precipitate of NO-*dimethylaporotioramine hydroxide* which crystallised from methanol in rather unstable, hygroscopic orange needles (0·5 g.), m. p. 180° (decomp.) (Found: N, 4·2; OMe, 7·9; NMe, 5·2. $C_{24}H_{33}O_3N$ requires N, 3·7; OMe, 8·1; NMe, 7·6%). Addition of hydriodic acid to a solution of this base in acetone regenerated quantitatively the parent iodide, m. p. and mixed m. p. 216° (decomp.), which was also obtained when the free base was refluxed in acetone solution with methyl iodide. When a solution of *NO*-dimethyl*apo*rotioramine hydroxide in methanol at 60° was treated with 2N-aqueous sodium hydroxide *N*-methyl*apo*rotioramine was formed in low yield.

Methylation of either *apo*rotioramine (0·5 g.) or *N*-methyl*apo*rotioramine (0·5 g.) with methyl sulphate–potassium carbonate in boiling acetone gave the methosulphate of *O*-dimethyl-*apo*rotioramine which separated from ethyl acetate in yellow needles (0·2 g.), m. p. 172°. The addition of 2N-aqueous sodium hydroxide to a solution of this methosulphate in methanol furnished *NO*-dimethyl*apo*rotioramine hydroxide in orange needles, m. p. and mixed m. p. 180° (decomp.).

(*c*) After *N*-methyl*apo*rotioramine hydriodide (1 g.) or *NO*-dimethyl*apo*rotioramine iodide (1 g.) had been heated with potassium carbonate (2 g.) and methyl iodide (2 ml.) in boiling acetone (100 ml.) for 6 hr., purification of the product from methanol gave a *substance* in yellow prisms (0·8 g.), m. p. 202° (decomp.), containing ionisable halogen (Found: C, 58·7, 59·1; H, 6·8, 6·8; N, 2·8, 2·6; OMe, 6·5, 7·3; NMe, 7·2; I, 25·5. $C_{25}H_{34}O_3NI$ requires C, 59·2; H, 6·7; N, 2·8; OMe, 6·1; NMe, 5·7; I, 25·0. $C_{24}H_{32}O_3NI$ requires C, 58·5; H, 6·5; N, 2·8; OMe, 6·3; NMe, 5·9; I, 25·7%). The mixed m. p. with *NO*-dimethyl*apo*rotioramine iodide was *ca.* 186° (decomp.).

*NO*-Dimethyl*apo*rotioramine iodide was recovered unchanged when treated with methyl sulphate–potassium carbonate in boiling acetone for 6 hr.

The ultraviolet absorption spectra were determined in 95% alcohol with a Unicam S.P. 500 Spectrophotometer whilst the infrared spectral data were obtained in Nujol by using a Perkin-Elmer Model 21 double-beam spectrophotometer. The analyses were by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

UNIVERSITY OF LIVERPOOL. [*Received, November 14th*, 1957.]

## 373. *The Chemistry of Fungi. Part XXXV.* A Preliminary Investigation of Ergoflavin.*

By G. Eglinton, F. E. King, G. Lloyd, J. W. Loder, J. R. Marshall, Alexander Robertson, and W. B. Whalley.

Ergoflavin, one of the colouring matters of ergot, has probably the molecular formula $C_{30}H_{26}O_{14}$, and not $C_{15}H_{14}O_7$, as previously suggested. The pigment contains four phenolic hydroxyl groups, two alcoholic hydroxyl groups, two carbonyl groups, and two γ-lactone rings. Degradation of the tetra-*O*-methyl ether with barium hydroxide furnishes a dimethyl ether of 3 : 3′-diacetyl-2 : 4 : 2′ : 4′-tetrahydroxydiphenyl, the structure of which has been substantiated by conversion into 3 : 3′-diethyl-2 : 4 : 2′ : 4′-tetramethoxydiphenyl, identical with a synthetic specimen.

In addition to the well-known alkaloids,[1] ergot, the sclerotia produced by the fungus *Claviceps purpurea* when grown on rye, contains 1—2% of colouring matter; although the bulk of the latter is amorphous the isolation of a number of pigments has been described, but in general the compounds have been inadequately characterised. Since the isolation [2] of the first crystalline yellow pigment in 1877 but little progress has been reported on the structural chemistry of the group.

A violet substance sclererythrin, the occurrence of which is limited to the walls of the cortical hyphæ, was isolated by Dragendorff and Podwyssotski [2] and the characteristic ultraviolet absorption spectrum of this pigment has been frequently utilised for the detection of ergot.[3,4,5] These authors [2] also obtained a brown amorphous substance, which according to Tschirch,[6] is impure sclererythrin, and described the isolation of the first crystalline yellow pigment, sclerocristallin, $C_{10}H_{10}O_4$, which was supposed to be reversibly convertible into another yellow pigment, scleroxanthin. Tschirch [7] claimed the isolation of crystalline scleroxanthin, but these pigments have not been further characterised and nothing is known concerning their chemistry; the uncharacterised amorphous, yellow pigment, Wenzell's ergoxanthin,[8] has been tentatively identified as scleroxanthin by Barger.[9] In 1897, Jacobj [10] isolated a neutral yellow crystalline pigment, ergochrysin, to which he allocated the formula, $C_{21}H_{22}O_9$. This substance was probably a lactone since it could be converted into an acidic hydrate, $C_{21}H_{24}O_{10}$.

By extraction of ergot with chloroform Kraft [11] in 1906 obtained a pigment, secalonic acid, $C_{14}H_{14}O_6$, in lemon-yellow needles, m. p. 244°, which dissolved readily in aqueous sodium carbonate with effervescence and gave a red-brown ferric reaction. Whilst the pigment could be recovered by the acidification of a freshly prepared solution in alkali, prolonged contact with alkaline reagents caused deep-seated decomposition. On being heated in a vacuum secalonic acid was converted into a non-acidic compound which however dissolved in warm alkali. From the alkaline solution an acidic product was precipitated by acid and Kraft suggested that both secalonic acid and the non-acidic transformation product were lactones. By purification of the yellow precipitate obtained by dilution of an ethereal extract of ergot with light petroleum, Barger [9] in 1931 isolated

* Part XXXIV, preceding paper.

[1] Barger, "Ergot and Ergotism," Gurney and Jackson, London, 1931.
[2] Dragendorff and Podwyssotski, *Arch. exp. Pathol. Pharmakol.*, 1877, **6**, 174.
[3] Tschirch, *Schweiz. Apoth.-Ztg.*, 1922, **60**, 1.
[4] *Idem*, *Pharm. Acta Helv.*, 1926, **1**, 89.
[5] *Idem*, "Handbuch der Pharmakognosie," Leipzig, 1923, Vol. III, p. 139.
[6] *Idem*, *Schweiz. Apoth.-Ztg.*, 1917, **65**, 345.
[7] Ref. 5, p. 156.
[8] Wenzell, *Amer. J. Pharm.*, 1910, **82**, 410.
[9] Ref. 1, p. 139.
[10] Jacobj, *Arch. exp. Pathol. Pharmakol.*, 1897, **39**, 104.
[11] Kraft, *Arch. Pharm.*, 1906, **244**, 336.

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ergochrysin, and suggested that this compound, scleroxanthin, and secalonic acid were identical, a claim which was supported by molecular-weight determinations on a sample of secalonic acid provided by Kraft.

In 1932 Bergmann [12] isolated ergochrysin from the residues obtained during the commercial production of ergot alkaloids. After removal of the ether-soluble impurities this compound was isolated by extraction with chloroform from which it separated in golden leaflets, m. p. 266°. Crystallised from alcohol–pyridine, the product, m. p. 242—244°, was solvated, and was transformed into the variety of m. p. 266° by recrystallisation from chloroform. Like Barger,[9] Bergmann [12] considered that his material, which was changed by dissolution in alkali into an amorphous material, was identical with secalonic acid and, on the basis of molecular-weight determinations by the Rast method, Kraft's $C_{14}$ formula for secalonic acid was doubled to $C_{28}H_{28}O_{12}$. Acetylation of ergochrysin with acetic anhydride–pyridine gave a low yield of a crystalline substance believed to be a deca-acetate, $C_{48}H_{48}O_{22}$, m. p. 240°; methylation failed to give a crystallisable product. Bergmann's major contribution to the chemistry of ergochrysin was the isolation of oxalic, acetic, and 3-hydroxy-5-methylbenzoic acid, resorcinol, and 2 : 4 : 2′ : 4′-tetrahydroxydiphenyl from a potassium hydroxide fusion of the pigment at 250—260°. This author, who concluded that the tetrahydroxydiphenyl was not an artefact derived from the resorcinol, also found that ergochrysin gave a crystalline nitro-compound, $C_{16}H_{15}O_9N$, m. p. 260°, by the action of nitric acid.

The next important contribution was by Stoll, Renz, and Brack, in 1952,[13] who isolated from Hungarian ergot a yellow crystalline acid which closely resembled secalonic acid, together with a second, closely associated acid, chrysergonic acid. These authors, who consider that their secalonic acid and Kraft's secalonic acid may not be identical with each other or with ergochrysin, showed that their secalonic acid and chrysergonic acid contained methoxyl groups and on the basis of methoxyl estimations revised the formula of secalonic acid to $C_{31}H_{30\text{-}32}O_{14}$, and allocated the formula $C_{32}H_{30\text{-}32}O_{14}$ to chrysergonic acid. Both compounds gave normal optical rotations in chloroform or acetone but in pyridine the rotation gradually changed to a constant value and the original pigment could not then be recovered. The same phenomenon occurred more rapidly in alkali. Both pigments gave colourless crystalline derivatives with acetic anhydride–pyridine, but analyses and molecular-weight estimations indicate that these were degradation products devoid of acetyl residues. The products from secalonic acid and chrysergonic acid, which were provisionally formulated as $C_{17}H_{16}O_7$ and $C_{15}H_{16}O_7$ respectively, still retained methoxyl groups, but were insoluble in alkali. On fusion with alkali the pigments furnished the same degradation products. The phenolic fraction contained 2 : 4 : 2′ : 4′-tetrahydroxydiphenyl, and the acid fraction succinic and methylsuccinic acid which were not obtained in the degradation of ergochrysin recorded by Bergmann.[12] Under milder conditions, *e.g.*, 50% alkali at 125°, the pigments gave only methylsuccinic acid. From these experiments Stoll *et al.*[13] concluded that secalonic and chrysergonic acid were closely related.

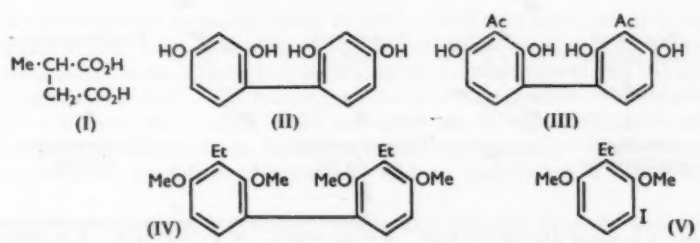
A comprehensive investigation on the ergot pigments is in progress in these laboratories. The present paper deals with our preliminary examination of ergoflavin. This was isolated in 1912 as yellow needles, m. p. 338° (decomp.), by Freeborn [14] who found that it was devoid of methoxyl groups and after intensive drying gave analytical and molecular-weight (Barger's vapour-pressure method [15]) values in agreement with the formula, $C_{15}H_{14}O_7$. Acetylation furnished what appeared to be a tetra-acetate, m. p. 231°, whence hydrolysis regenerated ergoflavin; fusion with alkali gave unidentified phenolic material. Forst [16] and Barger [1] repeated the isolation of ergoflavin, and Bergmann,[12] in his investigation of secalonic acid, obtained ergoflavin, m. p. 344°, and confirmed the $C_{15}$ formula.

[13] Bergmann, *Ber.*, 1932, **65**, 1486, 1489.
[13] Stoll, Renz, and Brack, *Helv. Chim. Acta*, 1952, **35**, 2022.
[14] Freeborn, *Pharm. J.*, 1912, **88**, 568.
[15] Barger, *J.*, 1904, **85**, 286.
[16] Forst, *Arch. exp. Pathol. Pharmakol.*, 1926, **114**, 125.

The Zerewitinoff method indicated the presence of five active hydrogen atoms and acetylation furnished a colourless tetra- or penta-acetate, m. p. 244°, probably identical with Freeborn's acetate, m. p. 231°. Though he failed to isolate crystalline methylation products with diazomethane or dimethyl sulphate Bergmann established that with dilute alkali ergoflavin gave a hydroxy-acid, ergoflavinic acid, $C_{15}H_{16}O_8$, which regenerated ergoflavin on being heated in water, indicating that ergoflavin was a lactone.

In the present work ergoflavin has been isolated from commercial fat residues together with a considerable quantity of a semi-crystalline material, concerning which we shall report later. Ergoflavin forms optically active, yellow needles, m. p. 350° (decomp.), which tenaciously retain solvent of crystallisation, give an intense green ferric reaction in alcohol, are devoid of methoxyl groups, do not furnish derivatives with the usual carbonly reagents, and are not hydrogenated under standard conditions. Most derivatives of ergoflavin retain solvent and do not readily give consistent analytical results. According to the Kuhn–Roth method ergoflavin appears to contain at least two *C*-methyl residues, and a determination of the molecular weight by the ebullioscopic method,[17] in acetone, indicates conclusively that the $C_{15}$ formula of Bergmann [12] and Freeborn [14] must be approximately doubled. Though from the several closely associated formulæ it is not possible at this stage to reach a final conclusion it appears that the formula $C_{30}H_{26}O_{14}$ for ergoflavin is in best accord with the analytical figures of the metabolite and its derivatives and will be used provisionally in the present paper. The accuracy of the molecular-weight estimations was checked against parallel determinations with 2 : 4 : 6 : 2′ : 4′-pentahydroxybenzophenone and is supported by the molecular-weights obtained for various derivatives of ergoflavin. The possibility that the green ferric reaction of ergoflavin is due to the presence of the catechol residue was investigated by using the characteristic pH change from 5 to 2 which occurs when a catechol is added to an aqueous solution of boric acid. Since the pH of a standard solution of boric acid was not influenced by the addition of ergoflavin it seems likely that this system is not present in ergoflavin and hence the characteristic ferric reaction may well be due to an *o*-hydroxycarbonyl moiety.

On oxidation with potassium permanganate ergoflavin gave methylsuccinic acid (I), and fusion with potassium hydroxide yielded acetic and methylsuccinic acid together with 2 : 4 : 2′ : 4′-tetrahydroxydiphenyl (II), the isolation of which in conjunction with the general properties of ergoflavin, indicates the presence of an aromatic kernel and a close structural affinity with ergochrysin and secalonic acid. Since resorcinol is not converted into the diphenyl (II) under the conditions of the alkaline fusion it is unlikely that this derivative is an artefact, a conclusion which is substantiated by work described below. The aromatic nature of ergoflavin is also inferred from its ready nitration to a dinitroergoflavin, $C_{30}H_{24}O_{14}(NO_2)_2$ whilst the resistance of the pigment to reduction with sodium and alcohol indicates the absence of a naphthalene system.



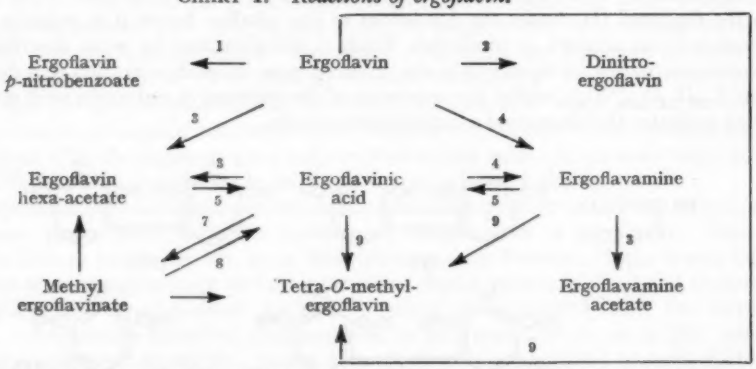

Ergoflavin exhibits the properties of a di-γ-lactone. Thus the infrared spectrum has an absorption band at 1790 cm.$^{-1}$ attributable to this system, and warm dilute potassium hydroxide solution converts the metabolite into a dibasic acid, ergoflavinic acid

[17] Glasstone, "A Textbook of Physical Chemistry," Macmillan, London, 1940, p. 629.

$C_{28}H_{28}O_{12}(CO_2H)_2$ (cf. Bergmann [12]), which is easily soluble in aqueous sodium hydrogen carbonate, readily regnerates ergoflavin in hot dilute acid, is devoid of the infrared band at 1790 cm.$^{-1}$, and exhibits absorption in the carbonyl region at 1740, 1660, 1620, and 1580 and in the acid region at 3600—3300 cm.$^{-1}$. With diazomethane ergoflavinic acid gives methyl ergoflavinate, $C_{28}H_{28}O_{12}(CO_2Me)_2$ [infrared bands at 3570, 3300, 3100, 1735 (aliphatic ester), 1670, 1620, and 1580 cm.$^{-1}$], which on hydrolysis with alkali regenerates ergoflavinic acid and on acetylation furnishes hexa-acetylergoflavin $C_{30}H_{20}O_8(OAc)_6$, identical with the acetylation product of ergoflavin (cf. Bergmann [12] and Freeborn [14]); deacetylation of this acetate with alkali regenerates ergoflavinic acid. Whilst ergoflavin readily furnishes a fully acetylated derivative (devoid of infrared absorption in the hydroxyl region) and a non-crystalline fully substituted *p*-nitrobenzoate (no hydroxyl absorption), it yields only a tetratoluene-*p*-sulphonate, $C_{58}H_{50}O_{22}S_4$, indicating that two of the hydroxylic functions may be subject to steric hindrance.

With methyl sulphate or iodide in acetone with potassium carbonate ergoflavin readily forms tetra-*O*-methylergoflavin, $C_{30}H_{22}O_{10}(OMe)_4$, which exhibits infrared absorption at 3525 (hydroxyl), 1800 (γ-lactone), 1690, 1600, and 1580 cm.$^{-1}$, is not readily soluble in aqueous alkali, has a negative ferric reaction, does not form carbonyl derivatives under the usual conditions, and by the Rast method in camphor and the micromolecular-distillation method [18] has a molecular weight in the region of 600. Consequently it seems likely that the four hydroxyl groups methylated by this process are phenolic (or enolic) and the remaining free hydroxyl groups are alcoholic. That two alcoholic groups are unmethylated is established by the formation of a di-*O*-acetate, $C_{30}H_{20}O_8(OMe)_4(OAc)_2$, and a di-*p*-nitrobenzoate, $C_{44}H_{28}O_{16}N_2(OMe)_4$, from tetra-*O*-methylergoflavin; both derivatives are devoid of hydroxyl absorption in the infrared spectrum. Tetra-*O*-methylergoflavin, which is also formed when methyl ergoflavinate is methylated with methyl sulphate–potassium carbonate in acetone, is unchanged by the prolonged action of diazomethane or by Purdie's reagents. In accordance with the formation from ergoflavin of only a tetratoluene-*p*-sulphonate, tetra-*O*-methylergoflavin does not react with toluene-*p*-sulphonyl chloride. Further, since tetra-*O*-methylergoflavin is not affected by polyphosphoric acid at 170° it is highly probable that the two alcoholic hydroxyl groups are not tertiary. These reactions are summarised in Chart 1.

CHART 1. *Reactions of ergoflavin.*




Reagents: 1, *p*-$NO_2{\cdot}C_6H_4{\cdot}COCl$–$C_5H_5N$. 2, Conc. $HNO_3$. 3, $Ac_2O$–$C_5H_5N$. 4, Aq. $NH_3$ (*d* 0·88). 5, Hydrolysis. 6, Hot $H_2O$. 7, $CH_2N_2$. 8, Aq. KOH. 9, $Me_2SO_4$–$K_2CO_3$.

On demethylation with hydriodic acid tetra-*O*-methylergoflavin regenerates ergoflavin, whilst hydrobromic acid gives rise to a di-*O*-methylergoflavin, $C_{20}H_{24}O_{12}(OMe)_2$, which is

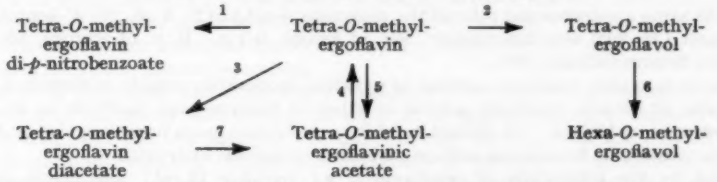
[18] Niederl, Kasanof, Kisch, and Subba Rao, *Mikrochem. Mikrochim. Acta*, 1949, **34**, 132.

identical (infrared spectrum) with the methylation product from ergoflavin with methyl sulphate and sodium hydrogen carbonate in boiling acetone and exhibits infrared bands at 1792 ($\gamma$-lactone) and 1603 cm.$^{-1}$ (*o*-hydroxycarbonyl). Methylation of ergoflavin with diazomethane furnished a mixture of tetra-*O*-methylergoflavin and tri-*O*-methylergoflavin, $C_{30}H_{23}O_{11}(OMe)_3$, having an intense green ferric reaction in alcohol and infrared absorption at 1808 ($\gamma$-lactone), 1632 (chelated carbonyl), and 1693 cm.$^{-1}$ (isolated carbonyl). These results indicate that ergoflavin contains two *o*-hydroxycarbonyl systems.

With alkali tetra-*O*-methylergoflavin gave a small yield of tetra-*O*-methylergoflavinic acid, $C_{28}H_{24}O_8(OMe)_4(CO_2H)_2$, which is more conveniently obtained by hydrolysis of di-*O*-acetyltetra-*O*-methylergoflavin. This acid [infrared absorption at 3600—3100 (acid), 1740, 1700, and 1600 cm.$^{-1}$] is very readily re-lactonised by heat, boiling water or acid, or attempted further methylation. Barium hydroxide degrades tetra-*O*-methylergoflavin to a dimethyl ether of 3 : 3′-diacetyl-2 : 4 : 2′ : 4′-tetrahydroxydiphenyl (III) having the characteristic green ferric reaction of ergoflavin. The constitution of this product was established by reduction and subsequent methylation of the product to 3 : 3′-diethyl-2 : 4 : 2′ : 4′-tetramethoxydiphenyl (IV), the synthesis of which was achieved by the Ullmann condensation of 3-ethyl-1-iodo-2 : 4-dimethoxybenzene (V). The production of the diphenyl derivative (III) under comparatively mild conditions conclusively indicates that the 2 : 4 : 2′ : 4′-tetrahydroxydiphenyl obtained from the fusion of ergoflavin with alkali is not an artefact and hence that ergoflavin contains this diphenyl system. Moreover, the isolation of this $C_{16}$ fragment provides collateral evidence in favour of the new molecular formula for ergoflavin proposed in this communication.

Reduction of tetra-*O*-methylergoflavin with excess of lithium aluminium hydride gives rise to tetra-*O*-methylergoflavol, $C_{30}H_{34}O_{10}(OMe)_4$, which exhibits strong hydroxyl absorption (3390 cm.$^{-1}$) but is devoid of lactone and carbonyl absorption and dissolves readily in cold 2N-aqueous sodium hydroxide. Methylation of this product gave hexa-*O*-methylergoflavol, $C_{30}H_{28}O_4(OMe)_6(OH)_4$. These reactions are summarised in Chart 2.

CHART 2. *Reactions of tetra-*O*-methylergoflavin.*




Reagents: 1, *p*-$NO_2{\cdot}C_6H_4{\cdot}COCl$–$C_5H_5N$. 2, $LiAlH_4$. 3, $Ac_2O$–$C_5H_5N$. 4, Heat. 5, Aq. KOH. 6, $Me_2SO_4$–$K_2CO_3$. 7, Hydrolysis.

Ergoflavin in aqueous ammonia slowly furnishes a red crystalline product, provisionally called ergoflavamide, which is readily soluble in cold 2N-aqueous sodium hydroxide without evolution of ammonia, although on boiling ammonia was evolved and the solution then contained ergoflavinic acid. The infrared spectrum of this product exhibits absorption at 3550—3200 (OH and NH?), 1780, 1650, and 1600 cm.$^{-1}$. On methylation with methyl sulphate–potassium carbonate in boiling acetone ergoflavamide yields tetra-*O*-methylergoflavin, with the evolution of ammonia, and on acetylation a nitrogen-containing acetate.

Thus ergoflavin contains a diphenyl nucleus and has four phenolic and two alcoholic hydroxyl groups, two $\gamma$-lactone groups, and two carbonyl groups; the remaining oxygen atoms are probably present in ether linkages. Further, it seems highly likely that the molecule of ergoflavin is symmetrical, produced in Nature by oxidative coupling of identical $C_{15}$ fragments (cf. the similar dracorubin [19]).

[19] Robertson, Whalley, and Yates, *J.*, 1950, 3117.

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## Experimental

*Ergoflavin.*—The alkaloid-free oil (1 part) obtained by extraction of ergot with ether, was diluted with light petroleum (b. p. 60—80°) (5 parts). The resulting gelatinous precipitate separated more readily on addition of small amounts of methanol. It was collected by filtration (filter-aid) or by centrifugation (without a filter-aid) and on being dried at room temperature was a yellow-brown solid; 50 gallons of oil furnished 0·5—1 kg. of solid. This product (100 g.) was added to acetone (200 ml.) containing hydrochloric acid (10 ml.) and 24 hr. later the solution was filtered (undissolved solid was discarded) and concentrated to *ca.* 40 ml. The thick, black viscous residue was extracted with ether (3 × 350 ml.) and on being kept for 24 hr. the extract deposited crude ergoflavin (7 g.). On being concentrated to 500 ml. the ethereal solution deposited more crude ergoflavin (1—2 g.) during 24 hr.; in the course of 2—3 weeks the residual liquors deposited an amorphous, bright yellow solid (5—10 g.).

When a solution of the crude ergoflavin (8 g.) in the minimum amount of hot acetone (*ca.* 50 ml.) was concentrated to *ca.* 20 ml. and diluted with warm methanol (200 ml.) the resulting dark green solution deposited ergoflavin (5—6 g.) which on repeated crystallisation from methanol, aqueous methanol, dioxan, or aqueous dioxan formed yellow needles, m. p. 350° (decomp.), $[\alpha]_D^{21}$ +37·5° (*c* 1·236 in acetone), $\lambda_{max.}$ 240, 260, 381 mμ ($E_{1\,cm.}^{1\%}$ 350, 346, 130 respectively) [Found: C, 58·8, 59·3, 58·6, 58·6, 58·7; H, 4·8, 4·9, 4·4, 4·7, 4·4; *C*-Me, 3·7; OMe, 0. $C_{30}H_{30}O_{14}$ requires C, 58·6; H, 4·9. $C_{30}H_{26}O_{14}$ requires C, 59·0; H, 4·3; (2) *C*-Me, 5·0%]. Vicininal hydroxyl test: a concentrated solution of boric acid had pH 5 and addition of catechol or di*iso*propyl catechol to this gave a solution of pH 2. With quinol or ergoflavin the boric acid solution had an unchanged pH of 5.

*Molecular weight.* This was determined ebullioscopically in acetone solution by Lansberger's method,[17] using the formula: rise in b. p. = (Mass of solute × 100*K*)/(vol. of solution × Mol. wt. of solute), *K* being taken as 22·2° for acetone.

The acetone was previously dried over potassium carbonate and distilled and the ergoflavin was dried at 100°/15 mm. or over phosphoric oxide. The following results were obtained:

(*A*) Wt. of ergoflavin, 0·5 g. B. p. of acetone, 56·38°. *M* (mean of three determinations), 642.

(*B*) Wt. of ergoflavin, 0·5 g. B. p. of acetone, 56·25°. *M* (mean of six determinations), 660.

With the same apparatus and solvent the molecular weight of 2 : 4 : 6 : 3′ : 4′-pentahydroxybenzophenone (*M*, 262) was determined: Wt. of ketone, 0·3 g. B. p. of acetone, 56·37°. *M* (mean of six determinations), 279.

Ergoflavin is readily soluble in acetone or pyridine, moderately soluble in methanol, alcohol, ethyl acetate, or dioxan, sparingly soluble in ether or benzene, and insoluble in 2N-aqueous sodium hydrogen carbonate. In alcohol it exhibits an intense green ferric reaction and forms a deep yellow solution in 2N-aqueous sodium carbonate or sodium hydroxide.

Prepared by the interaction of ergoflavin (1 g.), pyridine (3 ml.), and acetic anhydride (25 ml.) on the steam-bath during 30 min., the *hexa-acetate* separated from chloroform–light petroleum (b. p. 60—80°) in prisms (1·3 g.), m. p. 248—249° (decomp.), $[\alpha]_D^{20}$ +61·2° (*c* 0·62 in dioxan), $\lambda_{max.}$ 340, 338 mμ ($E_{1\,cm.}^{1\%}$ 343, 61 respectively) [Found: C, 57·5, 57·9, 56·9, 57·1, 57·1, 56·8, H, 4·7, 4·7, 5·0, 4·6, 4·7, 4·7. $C_{30}H_{20}O_8(OAc)_6$ requires C, 58·6; H, 4·4. $C_{30}H_{20}O_8(OAc)_6,H_2O$ requires C, 57·3; H, 4·5%]. The same acetate (310 mg.) was formed (*a*) when a mixture of ergoflavin (0·5 g.), sodium acetate (3 g.), and acetic anhydride (5 ml.) was heated in a sealed tube at 200—230° for 1 hr., (*b*) when ergoflavin (100 mg.), acetic anhydride (5 ml.), and sodium acetate (500 mg.) were heated under reflux for 1½ hr., or (*c*) when ergoflavin (1 g.), acetic anhydride (23 ml.), and pyridine (1 ml.) were refluxed for 5 hr. On being boiled with methanol (15 ml.) and 2N-aqueous sodium hydroxide (15 ml.) for 6 hr. this acetate (250 mg.) was hydrolysed and after removal of the alcohol in a vacuum the aqueous liquor was extracted once with ether and acidified. Purified from aqueous methanol the precipitate gave ergoflavinic acid (110 mg.) having m. p. and mixed m. p. 340° (decomp.) and the requisite infrared spectrum.

Prepared from ergoflavin (1 g.) and toluene-*p*-sulphonyl chloride (1·3 g.) in pyridine (10 ml.) at 0° for 2 days, *ergoflavin tetratoluene*-p-*sulphonate* separated from alcohol (sparingly soluble) in needles (0·7 g.), m. p. 231° (decomp.) (Found: C, 56·5; H, 4·6. $C_{58}H_{50}O_{22}S_4$ requires C, 56·8; H, 4·1%).

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*Dinitroergoflavin.*—Ergoflavin (1 g.) dissolved in concentrated nitric acid (25 ml.) at 20° in 15 min. The red solution was added to ice (50 g.) and on purification from methanol the precipitate gave *dinitroergoflavin* in prisms (1·1 g.), m. p. 260° (decomp.), $[\alpha]_D^{20}$ +66·5° (in EtOH) [Found (specimen dried at 15°): C, 48·4, 48·7; H, 4·2, 3·6; N, 3·8. Found (specimen dried at 120°/1 mm. for 5 hr.): C, 51·5; H, 3·5. $C_{30}H_{24}O_{14}(NO_2)_2$ requires C, 51·4; H, 3·4; N, 4·0. $C_{30}H_{24}O_{14}(NO_2)_2,2H_2O$ requires C, 48·9; H, 3·8; N, 3·8%].

*Ergoflavinic Acid.*—A mixture of ergoflavin (3 g.) and 2N-aqueous potassium hydroxide (100 ml.) was warmed on the steam-bath for 10 min. and the bright yellow solution cooled and acidified (Congo) with 5N-hydrochloric acid. The gelatinous precipitate was extracted with ethyl acetate (3 × 40 ml.), and the product purified from aqueous methanol, giving ergoflavinic acid in yellow needles (2·7 g.) m. p. *ca.*, 340° (decomp.), $[\alpha]_D^{15}$ +542·6° (*c* 2·0 in alcohol), $\lambda_{max.}$ 355, 370 mμ ($E_{1\,cm.}^{1\%}$ 351, 105 respectively) (Found, on specimen dried at 100°/1 mm.: C, 55·6; H, 4·8. Calc. for $C_{30}H_{30}O_{16}$: C, 55·8; H, 4·7%). Bergmann [13] records m. p. 340° (decomp.). This acid, which is readily soluble in 2N-aqueous sodium hydrogen carbonate, has an intense green ferric reaction in alcohol, and on recrystallisation from acetic acid regenerates ergoflavin. It is readily soluble in dioxan, but very sparingly soluble in benzene, ethyl acetate, ether, or chloroform.

Excess of ethereal diazomethane was added to a solution of ergoflavinic acid (1·5 g.) in acetone (50 ml.) followed 30 min. later by excess of light petroleum (b. p. 40—60°): a crystalline solid separated. Purified from methanol, this furnished *methyl ergoflavinate* in very pale yellow needles (1·23 g.), m. p. 300—315° (decomp.) [Found: C, 56·2, 56·4; H, 5·1, 5·1; OMe, 9·5, 9·6. $C_{30}H_{28}O_{14}(OMe)_2$ requires C, 56·9; H, 5·0; OMe, 9·2%].

Methylation of methyl ergoflavinate (1·56 g.) in boiling acetone (70 ml.) with potassium carbonate (6 g.) and methyl sulphate (3·5 ml.) for 6 hr. gave tetra-*O*-methylergoflavin (1·16 g.) [m. p. and mixed m. p.; infrared spectrum (see below)]. Treated with excess of diazomethane in dioxan (25 ml.) for 10 days, methyl ergoflavinate (0·7 g.) furnished tetra-*O*-methylergoflavin (0·1 g.) accompanied by much non-crystallisable material.

Methyl ergoflavinate (0·35 g.) with boiling acetic anhydride (15 ml.) and pyridine (1·5 ml.) for 25 min. furnished hexa-*O*-acetylergoflavin (0·35 g.), m. p. and mixed m. p. 248—249°, with the requisite infrared spectrum. A high yield of the same derivative was obtained with hot sodium acetate–acetic anhydride in 1 hr.

Methyl ergoflavinate (0·2 g.) was heated in boiling acetone (15 ml.) containing potassium carbonate (0·2 g.) for 6 hr. and the solvent removed in a vacuum. The residue was triturated with N-aqueous sodium hydrogen carbonate, leaving ergoflavin (0·1 g.) having the requisite m. p., mixed m. p., and infrared spectrum.

*Oxidation of Ergoflavin with Potassium Permanganate.*—Potassium permanganate (20 g.) in water (500 ml.) was added with cooling during 6 hr. to ergoflavin (4 g.), dissolved in acetone (250 ml.), and next day the solution was clarified with 2N-sulphuric acid (15 ml.) and the acetone removed in a vacuum. Exhaustive extraction of the aqueous liquors with ether gave a brown semi-crystalline acidic product (1·88 g.) which was esterified with ethanolic hydrogen chloride at 60° for 6 hr. The resulting mixed esters distilled at 2 mm., furnishing a pale yellow neutral oil (1·5 g.). Prepared from this product (0·2 g.) and phenylhydrazine (0·5 g.) at 100° for 5 min., the bisphenylhydrazide of oxalic acid formed needles, m. p. 259°, from alcohol (Found: C, 62·0; H, 5·4. Calc. for $C_{14}H_{14}O_2N_4$: C, 62·2; H, 5·2%).

The mixed esters were converted in the *p*-phenylphenacyl derivative in the usual manner and gave the bis-*p*-phenylphenacyl derivative of methylsuccinic acid, m. p. and mixed m. p. 181° (Found: C, 75·8; H, 5·2. Calc. for $C_{33}H_{28}O_6$: C, 76·1; H, 5·4%).

*Fusion of Ergoflavin with Alkali.*—Ergoflavin (2 g.) was added during 5 min. to molten potassium hydroxide (15 g.) at 190° in a nickel crucible in nitrogen. The frothing melt was kept at 190—200° for 10 min., cooled, dissolved in water (100 ml.), acidified (Congo-red) with hydrochloric acid, and exhaustively extracted with ether. After being washed with N-aqueous sodium hydrogen carbonate the extract was evaporated, leaving a phenol (0·3 g.) which could not be satisfactorily purified but on methylation in boiling acetone by methyl sulphate–potassium carbonate followed by distillation of the product at 1 mm. gave a neutral, viscous resin; crystallisation from ether then furnished 2 : 4 : 2′ : 4′-tetramethoxydiphenyl in prisms (0·1 g.), m. p. and mixed m. p. 97° [Found: C, 70·0; H, 6·5; OMe, 45·5. Calc. for $C_{12}H_6(OMe)_4$: C, 70·1; H, 6·6; OMe, 45·3%].

The solution from the alkali fusion was acidified (Congo-red) with sulphuric acid and distilled

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with steam until the distillate was neutral. The solid remaining after the evaporation of the neutralised distillate was converted into the *p*-phenylphenacyl derivative and on purification from methanol this furnished the derivative of acetic acid, m. p. and mixed m. p. 112° (Found: C, 75·3; H, 5·5. Calc. for $C_{16}H_{14}O_3$: C, 75·6; H, 5·6%).

The acid fraction from the alkaline fusion of ergoflavin (6 g.) was esterified with boiling 5% alcoholic hydrogen chloride for 2 hr. and the resultant ester distilled at 105°/18 mm. (1·5 g.). Further purification by distillation gave ethyl methylsuccinate, $n_D^{20}$ 1·4208 (Found: C, 56·6; H, 8·4. Calc. for $C_7H_{12}O_4$: C, 57·4; H, 8·6%; $n_D^{20}$ 1·4233). The identity of this ester was further confirmed by the preparation of the *p*-phenylphenacyl derivative, m. p. and mixed m. p. 180°. Variations of these fusion conditions gave inferior yields.

*Methylation of Ergoflavin.*—(*a*) Methylation of ergoflavin (5 g.) in boiling acetone (60 ml.) with potassium carbonate (15 g.) and methyl sulphate (10 ml.) was complete in 3½ hr. The filtered solution was evaporated in a vacuum and the residue treated with water (100 ml.). Next day the buff precipitate was purified from acetone–methanol and then from benzene–light petroleum (b. p. 60—80°), giving *tetra*-O-*methylergoflavin* in needles (4·8 g.), m. p. 282° (decomp.), $[\alpha]_D^{22}$ +28·6° (*c* 1·5 in $CHCl_3$), $\lambda_{max.}$ 252, 348 mμ ($E_{1cm.}^{1\%}$ 442, 85 respectively) [Found: C, 62·6, 61·6, 62·5, 62·4, 62·9, 63·0; H, 5·5, 5·3, 5·7, 5·3, 5·6; OMe, 18·5, 18·1, 18·4, 18·1. *M* (Rast), 605, 641 (by the micromolecular distillation method [18]) 635. Found (for specimen dried at 100°/4 mm. for 5 hr. and then at 140°/4 mm. for 1 hr.): C, 61·8, 61·8; H, 5·2, 5·3; OMe, 17·8, 17·9, 18·1. $C_{30}H_{22}O_{10}(OMe)_4$ requires C, 61·3; H, 5·1; OMe, 18·7%; *M*, 666]. Methylation of ergoflavin in acetone with methyl iodide–potassium carbonate at 20° for 12 days gave a 40% yield of tetra-*O*-methylergoflavin. Tetra-*O*-methylergoflavin has a negative ferric reaction in alcohol and does not react with the usual carbonyl reagents. Prepared quantitatively by the pyridine–acetic anhydride method at room temperature for 24 hr., *di*-O-*acetyltetra*-O-*methylergoflavin* separated from light petroleum (b. p. 60—80°)–chloroform in plates, m. p. 340° (decomp.) [Found: C, 60·5, 60·2, 60·0; H, 5·5, 5·4, 5·3; OMe, 16·9. $C_{34}H_{26}O_{12}(OMe)_4$ requires C, 60·8; H, 5·1; OMe, 16·5%]. The *di*-p-*nitrobenzoate* of tetra-*O*-methylergoflavin separated from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 192° (decomp.) [Found: C, 59·5; H, 4·5; N, 2·9, 2·9; OMe, 12·2. $C_{44}H_{28}O_{16}N_2(OMe)_4$ requires C, 59·8; H, 4·2; N, 2·9; OMe, 12·9%].

Demethylation of tetra-*O*-methylergoflavin (0·5 g.) with boiling hydriodic acid (8 ml.; *d* 1·7) and acetic acid (from 6 ml. of anhydride) for 1 hr. gave ergoflavin (0·32 g.), identical with an authentic specimen. When the demethylation of tetra-*O*-methylergoflavin (0·5 g.) was effected with boiling hydrobromic acid (5 ml.) and acetic acid (from 10 ml. of anhydride) for 1 hr., crystals rapidly separated from the initially clear solution. Purified from acetone–methanol, these gave *di*-O-*methylergoflavin* in yellow prisms (0·3 g.), m. p. 338° (decomp.), with an intense green ferric reaction in alcohol [Found: C, 59·9; H, 4·9; OMe, 7·7. $C_{30}H_{24}O_{12}(OMe)_2$ requires C, 60·0; H, 5·0; OMe, 9·7%]. Methylated by the methyl sulphate–potassium carbonate–acetone method this ether regenerated, in high yield, tetra-*O*-methylergoflavin, having the requisite m. p., mixed m. p. and infrared spectrum.

(*b*) A solution of ergoflavin (0·6 g.) in acetone (20 ml.) containing sodium hydrogen carbonate (2 g.) and methyl sulphate (2 ml.) was heated under reflux for 48 hr. On isolation in the usual manner the product was purified from acetone–methanol, giving (A) a substance (0·15 g.), m. p. 295° (decomp.), with a negative ferric reaction (possibly impure tetra-*O*-methylergoflavin), and (B) di-*O*-methylergoflavin in yellow prisms, m. p. 320—330° (decomp.), which has an intense green ferric reaction in alcohol and is identical with the product prepared by partial demethylation of tetra-*O*-methylergoflavin [Found: C, 59·0, 59·0; H, 5·2, 5·2; OMe, 10·6. Calc. for $C_{30}H_{24}O_{12}(OMe)_2$: C, 60·0; H, 5·0; OMe, 9·7%].

(*c*) A solution of ergoflavin (0·12 g.) in methanol (15 ml.) was treated with excess of ethereal diazomethane at 5° for 6 days. Purification of the product from acetone–methanol gave tetra-*O*-methylergoflavin (0·04 g.), m. p. and mixed m. p. 282° (decomp.), and *tri*-O-*methylergoflavin* in yellow needles (0·05 g.), m. p. 248—252° (decomp.), with an intense green ferric reaction in in alcohol [Found: C, 59·8; H, 5·3; OMe, 14·6. $C_{30}H_{23}O_{11}(OMe)_3$ requires C, 60·7; H, 5·0; OMe, 14·4%].

*Tetra*-O-*methylergoflavinic Acid.*—(*a*) A suspension of di-*O*-acetyltetra-*O*-methylergoflavin (5 g.) in methanol (100 ml.) and water (100 ml.) containing potassium hydroxide (10 g.) was heated under reflux for 6 hr.; a clear solution was formed after 45 min. The alcohol was removed in a vacuum and the residual solution acidified (Congo) with 5N-hydrochloric acid and

extracted with ethyl acetate. The ethyl acetate extract soon deposited crystals which on purification from methanol gave *tetra-O-methylergoflavinic acid* in rods (2·2 g.), m. p. 237—238° (decomp.) [Found: C, 54·1; H, 6·5; OMe, 17·2, 17·5. $C_{30}H_{26}O_{12}(OMe)_4$ requires C, 58·1; H, 5·4; OMe, 17·7. $C_{30}H_{26}O_{12}(OMe)_4,3H_2O$ requires C, 54·0; H, 5·9; OMe, 16·4%].

(*b*) A mixture of tetra-*O*-methylergoflavin (0·5 g.), methanol (30 ml.), water (30 ml.), and sodium hydroxide (2 g.) was boiled for 6 hr. and the alcohol was removed in a vacuum. The acidified solution was then extracted with ethyl acetate, and the product purified from methanol–ethyl acetate, giving slightly impure tetra-*O*-methylergoflavinic acid (0·1 g.).

Tetra-*O*-methylergoflavinic acid is readily soluble in 2N-aqueous sodium hydrogen carbonate, has a negative ferric reaction in alcohol, does not yield a 2 : 4-dinitrophenylhydrazone, and on being heated above its m. p. rapidly resolidifies by conversion into tetra-*O*-methylergoflavin which then melts at 280°. Re-lactonisation also occurs when tetra-*O*-methylergoflavinic acid is boiled in water or when a suspension of the acid (0·2 g.) in 5N-hydrochloric acid (25 ml.) was boiled for 1 hr. On isolation the crystalline product, m. p. 260—270° (0·17 g.), gave tetra-*O*-methylergoflavin, m. p. and mixed m. p. 282—283° with the requisite infrared spectrum, on purification.

*Alkaline Degradation of Tetra-O-methylergoflavin.*—A suspension of tetra-*O*-methylergoflavin (2 g.) in water (50 ml.), containing barium hydroxide octahydrate (25 g.), was heated under reflux for 5 hr., a clear orange solution being formed. The cooled, acidified hydrolysate was exhaustively extracted with ether, and the extract washed successively with 2N-aqueous sodium carbonate and 2N-aqueous sodium hydroxide, after which the ethereal solution did not contain a neutral fraction. Acidification of the carbonate washings gave an intractable precipitate (0·86 g.), but on being acidified the sodium hydroxide extract gave a product which was isolated with benzene and chromatographed from this solvent on silica gel. The benzene eluate furnished a *dimethyl ether* of 3 : 3′-diacetyl-2 : 4 : 2′ : 4′-tetrahydroxydiphenyl. This ether separated from light petroleum (b. p. 60—80°) in pale yellow plates (50 mg.), m. p. 168° [Found: C, 65·6; H, 5·6; OMe, 18·5; *C*-Me, 8·7; *M* (Rast), 333. $C_{14}H_6O_4(Me)_2(OMe)_2$ requires C, 65·4; H, 5·5; OMe, 18·8; *C*-Me, 9·1%; *M*, 330]. It has an intense green ferric reaction in alcohol. Extensive modification of the reaction conditions did not improve the yield of this phenol. The *dipiperonylidene derivative* separated from alcohol (sparingly soluble) in orange-red needles, m. p. 235° [Found: OMe, 10·3. $C_{32}H_{26}O_8(OMe)_2$ requires OMe, 10·4%].

With methyl sulphate–potassium carbonate in boiling acetone for 7 hr. this phenol furnished a quantitative yield of 3 : 3′-*diacetyl*-2 : 4 : 2′ : 4′-*tetramethoxydiphenyl* which separated from light petroleum (b. p. 60—80°) in needles, m. p. 138° [Found: C, 67·4; H, 6·2; OMe, 34·6. $C_{16}H_{10}O_2(OMe)_4$ requires C, 67·0; H, 6·2; OMe, 34·6%].

3 : 3′-*Diethyl*-2 : 4 : 2′ : 4′-*tetramethoxydiphenyl.*—(*a*) A mixture of the above dimethyl ether of 3 : 3′-diacetyl-2 : 4 : 2′ : 4′-tetrahydroxydiphenyl (170 mg.), 100% hydrazine hydrate (1 ml.), and diethylene glycol (6 ml.) was heated at 140—150° for ½ hr. A solution of potassium hydroxide (1 g.) in water (1 ml.) was then added and the mixture kept at 140—150° for a further ½ hr. and then slowly heated to 200° (without a condenser) and finally maintained at 200—210° for 2 hr. After isolation the crude product was methylated by methyl sulphate–potassium carbonate–acetone and the resulting ether purified from light petroleum (b. p. 40—60°), giving 3 : 3′-*diethyl*-2 : 4 : 2′ : 4′-*tetramethoxydiphenyl* in prisms (75 mg.), m. p. 109° [Found: C, 72·6; H, 8·3; OMe, 37·0. $C_{16}H_{14}(OMe)_4$ requires C, 72·7; H, 7·9; OMe, 37·6%].

(*b*) An agitated solution of 2-ethyl-1 : 3-dimethoxybenzene [20] (5·5 g.) in alcohol (25 ml.) was treated alternately with iodine (9 g.) and yellow mercuric oxide (5 g.), portionwise, and when decolorisation was complete the mixture was filtered into water, the salts were well washed with ether, and the excess of liquor was extracted with ether. Distillation of the combined extracts gave 2-ethyl-1 : 3-dimethoxybenzene (2—3 g.) and 3-*ethyl*-1-*iodo*-2 : 4-*dimethoxybenzene* (4 g.), b. p. 155—157°/13 mm. [Found: C, 41·0; H, 4·5; OMe, 20·8. $C_6H_7I(OMe)_2$ requires C, 41·1; H, 4·5; OMe, 21·2%]. A mixture of the iodo-compound (3·3 g.) and copper bronze (4 g.) was heated at 254° for 1½ hr., giving 3 : 3′-diethyl-2 : 4 : 2′ : 4′-tetramethoxydiphenyl which was isolated by extraction with light petroleum (b. p. 40—60°) and crystallised from methanol or light petroleum (b. p. 40—60°) as prisms, m. p. and mixed m. p. 109° and having the requisite infrared spectrum, [Found: C, 72·9; H, 8·1; OMe, 37·4. Calc. for $C_{16}H_{14}(OMe)_4$: C, 72·7; H, 7·9; OMe, 37·6%].

[20] Sprenger and Ruoff, *J. Org. Chem.*, 1946, **11**, 189.

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*Tetra-O-methylergoflavol.*—A solution of tetra-*O*-methylergoflavin (3 g.) in dioxan (20 ml.) was added dropwise to a suspension of lithium aluminium hydride (6 g.) in boiling ether (250 ml.), and the mixture then heated under reflux for 4 hr. On isolation in the usual manner the product gave *tetra-O-methylergoflavol* which separated from aqueous methanol in needles (1·9 g.), m. p. >320° (decomp.), $\lambda_{max.}$ 214, 260 mμ ($E^{1\%}_{1cm.}$ 840, 275) [Found (on specimen dried at 70°/0·01 mm. for 3 hr.): C, 57·7, 57·3; H, 7·3, 6·8; OMe, 17·8, 17·8. Found (on specimen dried at 140°/0·01 mm. for 21 hr.): C, 58·4, 58·7; H, 6·8, 6·9. $C_{30}H_{34}O_{10}(OMe)_4$ requires C, 60·2; H, 6·8; OMe, 18·5%; *M*, 578. $C_{30}H_{34}O_{10}(OMe)_4,H_2O$ requires C, 58·6; H, 6·9. $C_{30}H_{34}O_{10}(OMe)_4,2H_2O$ requires C, 57·0; H, 7·0; OMe, 17·3%. *M* (by micro-molecular distillation method [18]), 600]. This phenol is readily soluble in 2N-aqueous sodium hydroxide and has a negative ferric reaction in alcohol. Methylation of tetra-*O*-methylergoflavol (0·6 g.) with aqueous-methanolic 3N-potassium hydroxide and methyl sulphate at 60° furnished *hexa-O-methylergoflavol* as a semicrystalline solid (0·4 g.), m. p. 190° (decomp.), insoluble in 2N-aqueous sodium hydroxide [Found: C, 61·1, 60·2, 60·6, 60·5, 60·4; H, 7·9, 7·5, 7·4, 7·3, 7·3; OMe, 28·7, 27·1, 27·3, 27·4, 27·4. $C_{30}H_{32}O_8(OMe)_6$ requires C, 61·2; H, 7·1; OMe, 26·3%].

*Ergoflavamide.*—The yellow colour of a solution of ergoflavin (2 g.) in aqueous ammonia (*d* 0·88; 100 ml.) changed to deep red in 10—15 min., and 12 hr. later the cooled solution was acidified with 5N-aqueous hydrochloric acid. Rapid crystallisation of the gelatinous orange-red precipitate (2·3 g.) from aqueous methanol at 60° containing 2N-aqueous hydrochloric acid (5 drops) furnished *ergoflavamide* in red needles (1·8 g.), m. p. 340°, $[\alpha]_D^{23}$ +113·2° (in EtOH) (Found: C, 52·3, 52·2; H, 5·4, 5·6; N, 3·8, 3·5%). When a solution of ergoflavin (0·5 g.) in alcohol (100 ml.) was saturated with ammonia and the resulting red solution evaporated in a vacuum 48 hr. later, rapid crystallisation of the residual red solid from aqueous methanol gave ergoflavamide in red needles, m. p. and mixed m. p. 340° (Found: C, 51·2; H, 5·4; N, 2·9%).

Prolonged contact of the crude product with the solvent during purification reduces the yield of pure ergoflavamide. The amide is readily soluble in cold 2N-aqueous sodium hydroxide without the liberation of ammonia. When a solution of ergoflavamide (0·1 g.) in 10% aqueous sodium hydroxide (25 ml.) was boiled for 20 min. ammonia was evolved and acidification of the cooled hydrolysate gave ergoflavinic acid which separated from aqueous methanol in yellow plates, m. p. *ca.* 300°, having the requisite infrared spectrum, $[\alpha]_D^{21}$ +227·9° (in EtOH) (Found: C, 51·7; H, 5·0%). Methylation of ergoflavamide (0·3 g.) by methyl sulphate–acetone–potassium carbonate for 5 hr. proceeded with evolution of ammonia to furnish a semi-crystalline solid which was difficult to purify and had the infrared spectrum of tetra-*O*-methylergoflavin. Acetylation of ergoflavamide (0·2 g.) by pyridine–acetic anhydride at room temperature for 24 hr. gave a semi-crystalline *acetate*, m. p. *ca.* 200° (decomp.) [from chloroform–light petroleum (b. p. 60—80°)] (Found: C, 56·9; H, 4·8; N, 2·5%).

We thank Messrs. Burroughs Wellcome & Co. for generous supplies of ergot fat, Messrs. T. & H. Smith Ltd., Edinburgh, for the preparation of the crude concentrate from this fat, and Lankro Chemicals, Eccles, for certain extraction facilities provided through the courtesy of Dr. Kroch.

The ultraviolet absorption spectra were determined in alcohol using a Unicam S.P. 500 Spectrophotometer and the infrared data were obtained in Nujol on a Grubb-Parsons S3 double beam spectrophotometer and a Perkin-Elmer Model 21. The majority of the analyses were by Mr. A. S. Inglis, M.Sc. and his associates of the Department of Organic Chemistry, The University, Liverpool.

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## 374. *Formyl Compounds. Part II.**

By Ursula M. Brown, P. H. Carter, and Muriel Tomlinson.

The four *Bz*-formyl-2 : 3-diphenylindoles, three 2 : 3-dimethylindole-aldehydes, and 4-formyldiphenylamine have been prepared and characterised, and the yields of aldehyde obtained by decomposition of 1 : 2 : 3 : 4-tetrahydro-6-toluene-*p*-sulphon- and -6-*p*-nitrobenzenesulphon-hydrazidocarbonylcarbazole and their 9-methyl derivatives with sodium carbonate in glycol and sodium glycollate in glycol have been compared. Azines, acylhydrazones, and one diacylhydrazine have been found as by-products in the McFadyen and Stevens reaction.

The four *Bz*-formyl-2 : 3-diphenylindoles have been prepared by converting the corresponding known acids,[1] into toluene-*p*-sulphonhydrazides which were then heated with sodium carbonate in glycol (McFadyen and Stevens reaction [2]). Three of the four 2 : 3-dimethylindole aldehydes have been similarly prepared. The dimethylindole acids had previously been made by Verkade and Lieste [3] from 1-bromoethyl methyl ketone and the corresponding methyl aminobenzoates: we made them from ethyl methyl ketone carboxyphenylhydrazones by the Fischer reaction. Verkade and Lieste did not prove which was which of the two acids from methyl *m*-aminobenzoate, but from analogy with substituted aminobenzoic acids they suggested that the one with the higher m. p. is the 6-carboxylic acid. Analogy with other indole derivatives supports this view but attempts by Plant and Jones [4] to prove it failed. Efforts to prepare 2 : 3-dimethylindole-4(?)-carbohydrazide were unsuccessful and 4(?)-formyl-2 : 3-dimethylindole has not therefore been made.

The yields obtained were variable (see below), and, as in the carbazole series, were generally better for the hindered positions of the *Bz*-nucleus of the indole. For the 7-, 6-, 5-, and 4-formyldiphenylindole they were 85, 28, 11, and 22% respectively, and for the 7-, 6(?)-, and 5-formyldimethylindoles 60, 4, and 15% respectively.

The new aldehydes resemble those of the carbazole series: [5] common condensations proceed readily but no reactions were found with sodium hydrogen sulphite, Fehling's solution, ammoniacal silver nitrate, potassium cyanide (benzoin-type condensation), or strong alkali (Cannizzaro reaction). Some properties are summarised below:

| Indole | M. p. | Colour | Infrared absorption (cm.$^{-1}$) in Nujol paste: CO (stretching) | NH (stretching) |
|---|---|---|---|---|
| 7-Formyl-2 : 3-diphenyl- | 137—138° * | Yellow | 1665 | 3330 |
| 6- ,, ,, ,, | 187—188 | Yellow | 1660 | 3240 |
| 5- ,, ,, ,, | 208—210 | Colourless | 1670 | 3300 |
| 4- ,, ,, ,, | 204—205 | Yellow | 1655 | 3250 |
| 7- ,, -2 : 3-dimethyl- | 126—127 | Yellow | 1675 | 3370 |
| (?)6- ,, ,, ,, | 95—96 | V. pale yellow | 1681 | 3250 |
| 5- ,, ,, ,, | 137—139 | Colourless | 1670 | 3200 |

* There was evidence for an unstable form, m. p. 121—123°.

Decomposition of 2 : 3-diphenyl-5-toluene-*p*-sulphonhydrazidocarbonylindole produces much azine as well as aldehyde, and 2 : 3-dimethyl-5- and 2 : 3-dimethyl-6(?)-toluene-*p*-sulphonhydrazidocarbonylindole each gave the corresponding formyl-2 : 3-dimethylindole 2′ : 3′-dimethylindolylhydrazone, together with the expected aldehyde.

The formation of by-products in the McFadyen and Stevens aldehyde preparation is of

* Part I, *J.*, 1957, 2210.

[1] Coldham, Lewis, and Plant, *J.*, 1954, 4528.
[2] McFadyen and Stevens, *J.*, 1936, 584.
[3] Verkade and Lieste, *Rec. Trav. chim.*, 1946, **65**, 912.
[4] Plant and D. L. Jones, D. L. Jones, Thesis, Oxford, 1956 (unpublished).
[5] Carter, Plant, and Tomlinson, *J.*, 1957, 2210.

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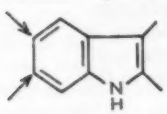
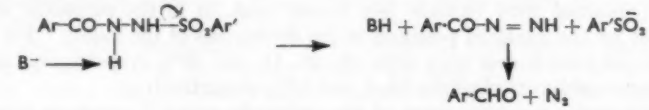
interest. Azines were found as products of decomposition of 1 : 2 : 3 : 4-tetrahydro-6- and 1 : 2 : 3 : 4-tetrahydro-7-toluene-*p*-sulphonhydrazidocarbonylcarbazole and possibly 3-toluene-*p*-sulphonhydrazidocarbonylcarbazole;[5] Dornow and Bormann[6] obtained the acylhydrazone as well as 2-methylnicotinic aldehyde from 3-benzenesulphonhydrazidocarbonyl-2-methylpyridine, and symmetrical diacylhydrazines were obtained from benzenepyrazinoylsulphonhydrazide[7] and 1-benzenesulphonhydrazidocarbonyl-4-nitrobenzene[8] (although the nature of the by-product was not proved in all cases). In the



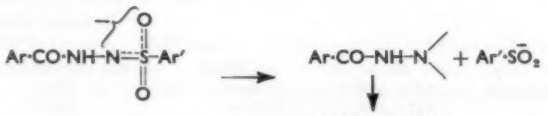
indole series we have found by-products only in positions not adjacent to the ring-junctions * (marked ⟶), which might suggest that steric, rather than electromeric, effects influence their formation or absence. We found, too, that whereas 1-benzenesulphonhydrazidocarbonylnaphthalene gave only 1-naphthaldehyde, yet 2-benzenesulphonhydrazidocarbonylnaphthalene afforded 2-naphthaldehyde together with some *NN'*-di-2-naphthoylhydrazine.

*N*-Benzoyl-4-toluene-*p*-sulphonhydrazidocarbonyldiphenylamine gives both 4-formyldiphenylamine and its azine. Albert[9] obtained 2-formyldiphenylamine in 80% yield from 2-toluene-*p*-sulphonhydrazidocarbonyldiphenylamine: he does not mention any by-product. The results in the diphenylamine series are therefore similar to those found with indoles and the presence of the NH group may be important. (We have not investigated the preparation of 3-formyldiphenylamine because diphenylamine-3-carboxylic acid has been made only by methods which give very poor yields[10,11] and our attempts to make it by a Chapman rearrangement did not succeed.)

Ingold *et al.*[12] have suggested that the McFadyen and Stevens reaction first involves a bimolecular elimination:




As sodium carbonate converts a sulphonhydrazide into its anion, it seems to us that the initial reaction may be more akin to the begining of the Hofmann degradation of a bromoamide ion in alkali:




Acylhydrazones could then arise by reduction of the $Ar{\cdot}CO{\cdot}N_2H$ fragment, perhaps with sulphinate, followed by condensation with aldehyde, but it seems difficult to explain the formation of azines without recourse to hydrolysis or solvolysis of $-CO{\cdot}NH-$ bonds: hydrolysis of $-NH{\cdot}SO_2-$ bonds in alkaline media seems unlikely.

In the hope of finding conditions that would produce optimum yields of aldehyde we have compared the amounts of aldehyde obtained when 1 : 2 : 3 : 4-tetrahydro-6-toluene-*p*-sulphon- and -6-*p*-nitrobenzenesulphon-hydrazidocarbonylcarbazole and their 9-methyl

* This might be further evidence for the view that the acid, m. p. 275—280°, is 6- (and not 4-)carboxy-2 : 3-dimethylindole.

[6] Dornow and Bormann, *Ber.*, 1949, **82**, 216.
[7] Fand and Spoerri, *J. Amer. Chem. Soc.*, 1952, **74**, 1345.
[8] Niemann and Hays, *ibid.*, 1943, **65**, 482.
[9] Albert, *J.*, 1948, 1230.
[10] Gilman, Van Ess, and Shirley, *J. Amer. Chem. Soc.*, 1944, **66**, 1214.
[11] Plant and Worthing, *J.*, 1955, 1278.
[12] Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093.

derivatives were decomposed by sodium carbonate or sodium glycollate in glycol. (These examples were chosen because here we had earlier [5] found particularly poor yields of aldehyde and much azine.) Percentage yields were as follows:

| | Toluene-*p*-sulphonhydrazido-derivative with sodium | | *p*-Nitrobenzenesulphonhydrazido-derivative with sodium | |
|---|---|---|---|---|
| | Carbonate | Glycollate | Carbonate | Glycollate |
| >NH ..... | 3·2 [5] | 30 | 22 | 10 |
| >NMe ..... | 5·4 [5] | 34 | 23 | 11 |

Some azine was found in all instances.

4-Formyldiphenylamine is now shown to be a pale yellow solid, m. p. 95—97°; it was earlier described [13] as a brown glass, m. p. about 70°. The *N*-benzoyldiphenylamine-4-carboxylic ester used as starting material was made from *p*-ethoxycarbonylphenyl *N*-phenylbenzimidate by a Chapman rearrangement: the *N*-benzoyl group was lost either during the McFadyen and Stevens reaction or on the alumina during purification of the aldehyde. As stated earlier, similar experiments designed to produce *N*-benzoyldiphenylamine-3-carboxylic esters afforded non-crystalline products. (3-Formyldiphenylamine does not appear to be known: attempts to make both it and its 4-isomer by Chapman rearrangement of the corresponding formylphenyl *N*-phenylbenzimidates were unsuccessful.)

Attempts to make acid chlorides from some of the indole acids mentioned above were successful only in the preparation of 7-chloroformyl-2 : 3-diphenylindole.

## Experimental

*Ethyl* 2 : 3-*Dimethylindole-7-carboxylate.*—*Ethyl methyl ketone* o-*carboxyphenylhydrazone* (23 g.) [yellow prisms, m. p. 140° (from methanol) (Found: C, 64·1; H, 6·7. $C_{11}H_{14}O_2N_2$ requires C, 64·1; H, 6·8%)] was boiled (1 hr.) with acetic acid (180 c.c.) and hydrochloric acid (56 c.c.). 2 : 3-Dimethylindole-7-carboxylic acid, m. p. 214—216°, separated from the cooled mixture and was converted into its *ethyl ester*, needles (from ethanol), m. p. 104—106° (Found: C, 71·7; H, 6·9. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·7%). Similarly, ethyl methyl ketone *p*-carboxyphenylhydrazone was converted into ethyl 2 : 3-dimethylindole-5-carboxylate, m. p. 110—113°, and *ethyl methyl ketone* m-*carboxyphenylhydrazone* (23 g.) [yellow plates, m. p. 140—141° (from acetic acid) (Found: C, 64·1; H, 7·0%)], boiled with acetic acid (160 c.c.) and hydrochloric acid (50 c.c.), gave, after 30 min., a mixture in which crystals began to appear. Cooling now afforded fairly pure 2 : 3-dimethylindole-6(?)-carboxylic acid (16 g.; m. p. 263—270°); methyl ester, m. p. 175—178° (Verkade and Lieste [3] give m. p. 275—280° and 180—181° for the acid and ester respectively). Dilution of the acetic–hydrochloric acid liquor gave a solid which was extracted with aqueous sodium carbonate to separate the required acid from 2 : 3-dimethylindole. The alkaline extract, on acidification, gave 2 : 3-dimethylindole-4(?)-carboxylic acid (5·5 g.; m. p. 173—177°); methyl ester, m. p. 61—63° (Verkade and Lieste give m. p. 189—190° and 64—65° for the acid and ester, respectively: we did not attempt further purification because the hydrazides are normally more easily purified than are the esters).

2 : 3-*Diphenylindole-7-carbohydrazide.*—Methyl 2 : 3-diphenylindole-7-carboxylate was refluxed with hydrazine (100%) for 5 hr. The *hydrazide* formed needles (from ethanol), m. p. 186—187° (Found: C, 76·7; H, 5·0. $C_{21}H_{17}ON_3$ requires C, 77·0; H, 5·2%). Similarly were made: the *6-carbohydrazide*, plates, m. p. 286—289° (from anisole) (Found: C, 76·7; H, 5·2%); the *5-carbohydrazide*, needles (from ethanol), m. p. 239° (Found: C, 76·8; H, 5·4%); and the *4-carbohydrazide*, prisms, m. p. 234° (from ethanol) (Found: C, 76·7; H, 5·0%); also 2 : 3-*dimethylindole-7-carbohydrazide*, prisms, m. p. 256—258° (from aqueous acetic acid) (Found: C, 64·7; H, 6·7. $C_{11}H_{13}ON_3$ requires C, 65·0; H, 6·4%); the corresponding 6(?)-*carbohydrazide*, prisms, m. p. 232—235° (from ethanol) (Found: C, 64·8; H, 6·5%); the *5-carbohydrazide*, m. p. 231—234° (from ethanol) (Found: C, 65·0; H, 6·3%); *N-benzoyldiphenylamine-4-carbohydrazide*, m. p. 201—202° (from ethanol) (Found: C, 68·9; H, 5·5. $C_{26}H_{17}O_2N_3.H_2O$ requires

[13] D.R.P. 103,578.

C, 68·5; H, 5·4%); naphthalene-1-carbohydrazide, needles, m. p. 164—166° (from ethanol) (Stolle and Zinsser [14] give m. p. 166°); naphthalene-2-carbohydrazide, needles, m. p. 147—148° (Pinner [15] gives m. p. 186° and Goldstein and Cornamusaz [16] give m. p. 147·5°). Attempts to prepare 2 : 3-dimethyl-4(?)-carbohydrazide failed: mild conditions left the ester unchanged, more vigorous treatment gave 2 : 3-dimethylindole.

2 : 3-*Diphenyl*-7-*toluene*-p-*sulphonhydrazidocarbonylindole*.—2 : 3-Diphenylindole-7-carbohydrazide (6 g.) and toluene-*p*-sulphonyl chloride (5·8 g.), kept in pyridine solution for 2 hr., afforded, after being poured into dilute hydrochloric acid, 2 : 3-*diphenyl*-7-*toluene*-p-*sulphonhydrazidocarbonylindole* (6·6 g.), needles, m. p. 237° (decomp.) (from acetic acid) (Found: S, 6·8. $C_{28}H_{23}O_3N_3S$ requires S, 6·7%). The following were similarly prepared from the above hydrazides and the appropriate sulphonyl chloride: the 6-*isomer*, prisms, m. p. 250—252° (decomp.) (from ethanol) (Found: C, 70·1; H, 5·0. $C_{28}H_{23}O_3N_3S$ requires C, 69·8; H, 4·8%); the 5-*isomer*, needles, m. p. 249—250° (decomp.) (from ethanol) (Found: C, 69·7; H, 5·0%); and the 4-*isomer*, prisms, m. p. 261° (decomp.) (from ethanol) (Found: C, 69·9; H, 5·0%); also 2 : 3-*dimethyl*-7-*toluene*-p-*sulphonhydrazidocarbonylindole*, prisms, m. p. 232° (decomp.) (Found: C, 60·2; H, 5·2. $C_{18}H_{19}O_3N_3S$ requires C, 60·5; H, 5·3%); 2 : 3-*dimethyl*-6(?)-*toluene*-p-*sulphonhydrazidocarbonylindole*, prisms, m. p. 193° (decomp.) (from aqueous ethanol) (Found: C, 60·4; H, 5·1%); and the 5-*isomer*, prisms, m. p. 245—246° (decomp.) (from ethanol) (Found: C, 60·5; H, 5·3%); 1-*benzenesulphonhydrazidocarbonylnaphthalene*, needles, m. p. 218—219° (decomp.) (from ethanol) (Found: C, 62·7; H, 4·2. $C_{17}H_{14}O_3N_2S$ requires C, 62·6; H, 4·3%); 2-*benzenesulphonhydrazidocarbonylnaphthalene*, needles, m. p. 189° (decomp.) (from ethanol) (Found: C, 62·9; H, 4·3; N, 8·6. $C_{17}H_{14}O_3N_2S$ requires C, 62·6; H, 4·3; N, 8·6%); N-*benzoyl*-4-*toluene*-p-*sulphonhydrazidocarbonyldiphenylamine*, prisms, m. p. 197—198° (decomp.) (from acetic acid) (Found: C, 66·5; H, 4·9. $C_{27}H_{23}O_4N_3S$ requires C, 66·8; H, 4·7%); 1 : 2 : 3 : 4-*tetrahydro*-6-p-*nitrobenzenesulphonhydrazidocarbonylcarbazole*, yellow prisms, m. p. 231—233° (decomp.) (from acetic acid) (Found: C, 54·8; H, 4·3. $C_{19}H_{18}O_5N_4S$ requires C, 55·1; H, 4·3%); and the 9-*methyl homologue*, prisms, m. p. 219—221° (decomp.) (from acetic acid) (Found: C, 55·9; H, 4·6. $C_{20}H_{20}O_5N_4S$ requires C, 56·1; H, 4·7%).

7-*Formyl*-2 : 3-*diphenylindole*.—2 : 3-Diphenyl-7-toluene-*p*-sulphonhydrazidocarbonylindole (18 g.) in dry ethylene glycol (150 c.c.) at 160° was treated with anhydrous sodium carbonate (24 g.) and after 2 min. the mixture was poured into water. The solid was collected, dried, dissolved in benzene, and chromatographed on alumina. 7-*Formyl*-2 : 3-*diphenylindole* (8·5 g.) was obtained as yellow plates, m. p. 138—139°, sintering at 121—123° (from ethanol) (Found: C, 84·6; H, 4·9; N, 4·7. $C_{21}H_{15}ON$ requires C, 84·8; H, 5·0; N, 4·7%). It formed a p-*nitrophenylhydrazone*, red needles, m. p. 240—241° (from acetic acid) (Found: C, 75·0; H, 4·7. $C_{27}H_{20}O_2N_4$ requires C, 75·0; H, 4·6%); a *semicarbazone*, needles, m. p. 209—210° (from ethanol) (Found: C, 74·8; H, 5·2. $C_{22}H_{18}ON_4$ requires C, 74·6; H, 5·1%); and an *anil*, yellow needles, m. p. 157—159° (from ethanol) (Found: C, 86·9; H, 5·6. $C_{27}H_{20}N_2$ requires C, 87·1; H, 5·4%). It condensed with nitromethane (in methanol with sodium hydroxide) to form 7-2′-*nitrovinyl*-2 : 3-*diphenylindole*, red needles, m. p. 197° (from acetic acid) (Found: C, 77·9; H, 4·7. $C_{23}H_{16}O_2N_2$ requires C, 77·6; H, 4·7%); and with malonic acid in pyridine giving 7-2′-*carboxyvinyl*-2 : 3-*diphenylindole*, yellow needles, m. p. 198° (from acetic acid) (Found: C, 81·2; H, 5·2. $C_{23}H_{17}O_2N$ requires C, 81·4; H, 5·0%). The oxime failed to crystallise but gave 7-*cyano*-2 : 3-*diphenylindole* when it was boiled with acetic anhydride (40 min.). This crystallised from benzene as prisms, m. p. 221—223° (Found: C, 85·4; H, 4·9. $C_{21}H_{14}N_2$ requires C, 85·7; H, 4·8%). With dimethylaniline (0·5 g.) and zinc chloride (0·2 g.) at 140—150° for 4 hr. this aldehyde (0·5 g.) gave *bis*-p-*dimethylaminophenyl*-2 : 3-*diphenylindol*-7-*ylmethane*, which crystallised from ethanol as plates, m. p. 189—190° (Found: C, 85·0; H, 6·7. $C_{37}H_{35}N_3$ requires C, 85·2; H, 6·7%). Oxidation with lead dioxide gave a blue-green dye. 7-Formyl-2 : 3-diphenylindole failed to acetylate and its solution in concentrated sulphuric acid was brownish-green.

6-*Formyl*-2 : 3-*diphenylindole*.—The corresponding sulphonhydrazide (8·5 g.) afforded, on decomposition as above, 6-*formyl*-2 : 3-*diphenylindole* (1·5 g.), yellow needles, m. p. 187—188° (from benzene) (Found: C, 85·0; H, 5·2; N, 4·5. $C_{21}H_{15}ON$ requires C, 84·5; H, 5·0; N, 4·7%). It gave a 2 : 4-*dinitrophenylhydrazone*, red prisms, m. p. 304—307° (decomp.) (Found:

[14] Stolle and Zinsser, *J. prakt. Chem.*, 1906, **74**, 19.
[15] Pinner, *Annalen*, 1897, **298**, 37.
[16] Goldstein and Cornamusaz, *Helv. Chim. Acta*, 1932, **15**, 939.

XUM

C, 68·2; H, 3·9. $C_{17}H_{19}O_4N_5$ requires C, 67·9; H, 4·0%); an *azine*, yellow-orange needles, m. p. 280—282° (Found: N, 9·5. $C_{42}H_{30}N_4$ requires N, 9·5%); and an *anil*, yellow prisms, m. p. 199—200° (from ethanol) (Found: N, 7·2. $C_{27}H_{20}N_2$ requires N, 7·5%). From it also were prepared **6-2′-*benzoylvinyl*-2 : 3-*diphenylindole***, orange needles, m. p. 242—243° (from ethanol) (Found: C, 86·6; H, 5·4; N, 3·5. $C_{29}H_{21}ON$ requires C, 87·2; H, 5·3; N, 3·5%), by condensation with acetophenone in alcoholic sodium hydroxide solution, and **6-2′-*acetylvinyl*-2 : 3-*diphenylindole***, orange needles, m. p. 210—212° (from ethanol) (Found: C, 85·4; H, 5·6. $C_{24}H_{19}ON$ requires C, 86·4; H, 5·7%), by interaction with acetone and sodium hydroxide.

**5-*Formyl*-2 : 3-*diphenylindole***.—The corresponding sulphonhydrazide (20 g.), decomposed as above, afforded **5-*formyl*-2 : 3-*diphenylindole*** (1·4 g.), prisms, m. p. 208—210° (from benzene) (Found: C, 84·8; H, 5·1; N, 4·9. $C_{31}H_{15}ON$ requires C, 84·8; H, 5·0; N, 4·7%). Solid (2·2 g.), insoluble in benzene, was recrystallised from anisole and yielded the *azine* of this aldehyde, prisms, m. p. 329—330°, not depressed by admixture with a specimen made from the aldehyde and hydrazine in ethanol (Found: C, 85·3; H, 5·0; N, 9·2. $C_{42}H_{30}N_4$ requires C, 85·4; H, 5·1; N, 9·5%). This aldehyde gave a **2 : 4-*dinitrophenylhydrazone***, red prisms, m. p. 305—306° (decomp.) (Found: C, 68·0; H, 4·2. $C_{27}H_{19}O_4N_5$ requires C, 67·9; H, 4·0%); a **p-*nitrophenylhydrazone***, orange prisms, m. p. 252—254° (from aqueous ethanol) (Found: C, 74·9; H, 4·9. $C_{27}H_{20}O_2N_4$ requires C, 75·0; H, 4·6%); a ***semicarbazone***, prisms, m. p. 332—335° (from anisole) (Found: C, 74·2; H, 5·1. $C_{32}H_{19}ON_4$ requires C, 74·6; H, 5·1%); and an *anil*, prisms, m. p. 185—186° (from ethanol) (Found: C, 86·9; H, 5·4. $C_{27}H_{20}N_2$ requires C, 87·1; H, 5·4%). From it was made **5-2′-*acetylvinyl*-2 : 3-*diphenylindole***, yellow prisms, m. p. 240—241° (from ethanol) (Found: C, 85·1; H, 5·8. $C_{24}H_{19}ON$ requires C, 85·4; H, 5·7%). It dissolved in sulphuric acid to form a brick-red solution, it could not be acetylated or methylated, and condensation products with nitromethane and malonic acid did not crystallise.

**4-*Formyl*-2 : 3-*diphenylindole***.—The corresponding sulphonhydrazide (3·7 g.) gave **4-*formyl*-2 : 3-*diphenylindole*** (0·5 g.), yellow prisms, m. p. 204—205° (from benzene) (Found: C, 85·1; H, 5·2; N, 4·4. $C_{31}H_{15}ON$ requires C, 84·8; H, 5·0; N, 4·7%). It formed a **2 : 4-*dinitrophenylhydrazone***, red prisms, m. p. 310—312° (decomp.) (Found: C, 67·7; H, 4·0. $C_{27}H_{19}O_4N_5$ requires C, 67·9; H, 4·0%); and an ***azine***, yellow prisms, m. p. 310—312° (Found: N, 9·0. $C_{42}H_{30}N_4$ requires N, 9·5%).

**7-*Formyl*-2 : 3-*dimethylindole***.—The sulphonhydrazide (8·5 g.) gave **7-*formyl*-2 : 3-*dimethylindole*** (2·5 g.), yellow needles, m. p. 126—127° (from ethanol) (Found: C, 76·4; H, 6·2; N, 7·8. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·3; N, 8·1%). It formed a **2 : 4-*dinitrophenylhydrazone***, red prisms, m. p. 279—281° (decomp.) (Found: C, 57·4; H, 4·5. $C_{17}H_{15}O_4N_5$ requires C, 57·5; H, 4·2%); a **p-*nitrophenylhydrazone***, red prisms, m. p. 212—213° (from ethanol) (Found: C, 66·5; H, 5·4. $C_{17}H_{16}O_2N_4$ requires C, 66·2; H, 5·2%); a ***semicarbazone***, needles, m. p. 220—222° (from ethanol) (Found: C, 62·9; H, 6·1. $C_{12}H_{14}ON_4$ requires C, 62·6; H, 6·1%); an ***azine***, yellow prisms, m. p. 269—271° (Found: N, 16·2. $C_{22}H_{22}N_4$ requires N, 16·4%); an *anil*, yellow needles, m. p. 74—75° (from ethanol) (Found: C, 82·1; H, 6·5. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·4%); and an *oxime*, needles, m. p. 99—100° (from ethanol) (Found: C, 70·3; H, 6·4. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4%). **7-*Cyano*-2 : 3-*dimethylindole***, yellow needles, m. p. 158—160° (from light petroleum, b. p. 60—80°) (Found: C, 77·1; H, 5·7. $C_{11}H_{10}N_2$ requires C, 77·6; H, 5·9%), was made by action of acetic anhydride on the oxime. With acetone this aldehyde gave **7-2′-*acetylvinyl*-2 : 3-*dimethylindole***, yellow prisms, m. p. 182—183° (from ethanol) (Found: C, 78·6; H, 7·3; N, 6·6. $C_{14}H_{15}ON$ requires C, 78·9; H, 7·0; N, 6·6%); with nitromethane **2 : 3-*dimethyl*-7-2′-*nitrovinylindole***, red prisms, m. p. 240—242° (from ethanol) (Found: C, 66·6; H, 5·7. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6%) was obtained; and it condensed with malonic acid to give **7-2′-*carboxyvinyl*-2 : 3-*dimethylindole***, brown prisms, m. p. 219—220° (decomp.) (from dilute acetic acid) (Found: C, 72·9; H, 5·9. $C_{13}H_{12}O_2N$ requires C, 72·6; H, 6·0%). It formed a pale yellow solution in sulphuric acid.

**6-*Formyl*-2 : 3-*dimethylindole***.—The corresponding sulphonhydrazide (5 g.) afforded **6-*formyl*-2 : 3-*dimethylindole*** (0·1 g. approx.), pale yellow prisms, m. p. 95—96° (from benzene) (Found: C, 76·2; H, 6·1; N, 8·2. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·3; N, 8·1%). It formed a **2 : 4-*dinitrophenylhydrazone***, brick-red prisms, m. p. >340° (decomp.) (Found: C, 57·8; H, 4·5. $C_{17}H_{15}O_4N_5$ requires C, 57·8; H, 4·2%). This aldehyde was unstable and difficult to elute and its solutions soon became red. Solid (1·5 g.), obtained with the aldehyde, crystallised from nitrobenzene and afforded **6-*formyl*-2 : 3-*dimethylindole* 2′ : 3′-*dimethylindolyl*-6′-*carbonylhydrazone***, yellow prisms, m. p. 309—313° (Found: C, 73·5; H, 6·3. $C_{22}H_{22}ON_4$ requires C,

73·8; H, 6·1%). This was identical (mixed m. p. and infrared absorption) with a specimen prepared by refluxing equivalent quantities of 6-formyl-2 : 3-dimethylindole and 2 : 3-dimethylindole-6-carbohydrazide in ethanol.

*5-Formyl-2 : 3-dimethylindole.*—The sulphonhydrazide (15 g.) gave *5-formyl-2 : 3-dimethylindole* (1·05 g.), prisms, m. p. 137—139° (from benzene) (Found: C, 76·4; H, 6·4; N, 8·1. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·4; N, 8·1%). Solid (2 g.), also produced during the decomposition of the sulphonhydrazide, gave prisms (from nitrobenzene), m. p. 314—317°, of *5-formyl-2 : 3-dimethylindole 2′ : 3′-dimethyl-5′-indolylcarbonylhydrazone.* This was identical (mixed m. p. and infrared absorption) with a synthesised specimen, m. p. 320—323°, prepared as above (Found: C, 73·7; H, 6·3. $C_{22}H_{22}ON_4$ requires C, 73·8; H, 6·1%). 5-Formyl-2 : 3-dimethylindole gave a *2 : 4-dinitrophenylhydrazone*, red plates, m. p. 290° (decomp.) (Found: C, 58·1; H, 4·5. $C_{17}H_{15}O_4N_5$ requires C, 57·8; H, 4·2%); an *azine*, yellow prisms, m. p. 333—334° (Found: C, 76·7; H, 6·6; N, 16·2. $C_{22}H_{22}N_4$ requires C, 77·2; H, 6·4; N, 16·4%); and an *anil*, pale yellow plates, m. p. 165—166° (from ethanol) (Found: C, 82·0; H, 6·4; N, 11·4. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·4; N, 11·3%). With acetone it gave *5-2′-acetylvinyl-2 : 3-dimethylindole*, yellow needles, m. p. 147—148° (from aqueous ethanol) (Found: N, 6·6. $C_{14}H_{15}ON$ requires N, 6·6%).

*1-Formylnaphthalene.*—1-Benzenesulphonhydrazidocarbonylnaphthalene (10 g.) was decomposed in ethylene glycol (100 c.c.) with dry sodium carbonate (6·5 g.) at 160° for 2 min. The solution obtained by pouring this mixture into water was extracted with ether which was then shaken with saturated sodium hydrogen sulphite solution: 1-formylnaphthalene sodium bisulphite compound (7·3 g.; equivalent to a yield of about 90%) was obtained. The aldehyde had b. p. 153/12 mm.

*2-Formylnaphthalene.*—The sulphonhydrazide (7·5 g.) was decomposed as above. The ether extract yielded 2-formylnaphthalene [(3 g.), needles (from aqueous methanol), m. p. 58°], and a small amount of solid, insoluble in ether, was recrystallised (twice) from ethanol, forming prisms, m. p. 238—240°, of *NN′*-di-2-naphthoylhydrazine (Found: C, 77·5; H, 5·1; N, 7·9. Calc. for $C_{22}H_{16}O_2N_2$: C, 77·6; H, 4·7; N, 8·2%). The m. p. was not depressed by admixture with a synthetic specimen, m. p. 242—243° (Goldstein and Cornamusaz [16] give m. p. 241°): the mixed m. p. with formylnaphthalene azine (m. p. 232°) was depressed. 2-Formylnaphthalene forms a *hydrazone*, prisms, m. p. 149—151° (from ethanol) (Found: C, 78·2; H, 6·1; N, 16·2. $C_{11}H_{10}N_2$ requires C, 77·6; H, 5·9; N, 16·5%).

† *4-Formyldiphenylamine.*—(i) *N*-Benzoyl-4-toluene-*p*-sulphonhydrazidocarbonyldiphenylamine (5 g.) in ethylene glycol (20 c.c.) was decomposed with sodium carbonate (12 g.) (2 min. at 160°). The solution was diluted and extracted with benzene, and chromatography of the benzene extract on alumina gave *4-formyldiphenylamine* (0·65 g.), light yellow needles, m. p. 95—97° (from benzene) (Found: C, 79·0; H, 5·8. $C_{13}H_{11}ON$ requires C, 79·2; H, 5·6%). *4-Formyldiphenylamine azine* (about 0·2 g.) was obtained partly as a precipitate and partly from the final runnings of the column. It separated from alcohol as yellow plates, m. p. 231—233°, identical (mixed m. p. and infrared absorption) with a synthetic specimen (Found: C, 79·8; H, 5·7. $C_{26}H_{22}N_4$ requires C, 80·0; H, 5·6%). (ii) Decomposition of the above sulphonhydrazide (5 g.) in glycol (20 c.c.) at 160° by adding sodium (1 g.) in glycol (20 c.c.), also at 160°, and dilution with water after 2 min. afforded 4-formyldiphenylamine (0·95 g.) and azine (about 0·2 g.). *4-Formyldiphenylamine 2 : 4-dinitrophenylhydrazone* forms red prisms, m. p. 243—245° (from acetic acid) (Found: C, 60·5; H, 4·2. $C_{19}H_{15}O_4N_5$ requires C, 60·5; H, 4·0%); and the *semicarbazone* forms plates, m. p. 220—223° (from ethanol) (Found: C, 66·1; H, 5·7. $C_{14}H_{14}ON_4$ requires C, 66·1; H, 5·7%).

*6-Formyl-1 : 2 : 3 : 4-tetrahydrocarbazole.*—(*a*) The toluene-*p*-sulphonhydrazide (4 g.) in ethylene glycol (25 c.c.) was treated at 160° with sodium (2 g.) in glycol (25 c.c.) at 160°. The solution was diluted after 2 min. and worked up as usual, yielding the aldehyde (0·65 g.), m. p. 142—144°. (*b*) Decomposition of 1 : 2 : 3 : 4-tetrahydro-6-*p*-nitrobenzenesulphonhydrazidocarbonylcarbazole (3 g.) in glycol (20 c.c.) with sodium carbonate (6 g.) for 2 min. at 160° gave aldehyde (0·15 g.), m. p. 142—144°. (*c*) Decomposition of the *p*-nitrobenzenesulphonhydrazide (3 g.) as under (*a*) above gave aldehyde (0·31 g.), m. p. 142—144°. Azine (about 0·5 g.) was obtained in each case.

*6-Formyl-1 : 2 : 3 : 4-tetrahydro-9-methylcarbazole.*—(*d*) Decomposition of the corresponding *p*-toluenesulphonhydrazide (5 g.) as in (*c*) above gave 6-formyltetrahydro-9-methylcarbazole (0·97 g.), m. p. 94—95°. (*e*) Decomposition of the *p*-nitrobenzenesulphonhydrazide (3 g.) as

under (*b*) gave aldehyde (0·16 g.), m. p. 94—95°. (*f*) Decomposition of the *p*-nitrosulphonhydrazide (3 g.) as under (*a*) above gave aldehyde (0·34 g.), m. p. 94—95°. Again azine was isolated in each case.

† p-*Ethoxycarbonylphenyl* N-*Phenylbenzimidate*.—Benzanilide (85·6 g.; dried at 100° for 5 hr.) was suspended in dry toluene (400 c.c.) and treated with phosphorus pentachloride (89 g.). After being heated at 100° until evolution of hydrogen chloride ceased (1 hr.), the solution formed was evaporated under reduced pressure. The *N*-phenylbenzimidoyl chloride, which solidified, was dissolved in dry ether (320 c.c.) and filtered slowly into a solution of ethyl *p*-hydroxybenzoate (78·6 g.) in ethanol (320 c.c.) in which sodium (16 g.) had been previously dissolved. The mixture was well stoppered: sodium chloride separated. The solvents were removed by distillation next day; the resulting oil was washed with water; it solidified to give p-*ethoxycarbonylphenyl* N-*phenylbenzimidate*, prisms (from ethanol), m. p. 83—85° (Found: C, 76·6; H, 5·5. $C_{22}H_{19}O_3N$ requires C, 76·6; H, 5·5%). The corresponding p-*methoxycarbonyl-compound*, made by using methyl *p*-hydroxybenzoate in methanol, crystallised in the original reaction mixture, and recrystallised from methanol as prisms, m. p. 107° (Found: C, 76·1; H, 5·3. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·1%).

† N-*Benzoyl*-4-*methoxycarbonyldiphenylamine*.—After the above methyl ester (9 g.) had been heated at 270—280° for 2 hr. it cooled to form a glass which crystallised in contact with methanol, from which it was then recrystallised. N-*Benzoyl*-4-*methoxycarbonyldiphenylamine* (7·3 g.) was obtained as prisms, m. p. 107—108°, depressed to 90° by admixture with the starting material (Found: C, 76·1; H, 5·2. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·1%). The corresponding *ethoxycarbonyl compound* separated from ethanol as prisms, m. p. 99—101° (Found: C, 76·5; H, 5·7. $C_{22}H_{19}O_3N$ requires C, 76·6; H, 5·5%).

† m-*Carboxyphenyl* N-*Phenylbenzimidate*.—Methyl *m*-hydroxybenzoate was condensed with *N*-phenylbenzimidoyl chloride (as above) but the product did not crystallise. Agitation with aqueous alcoholic potash for 3 hr. at room temperature gave a solution from which acid precipitated m-*carboxyphenyl* N-*phenylbenzimidate*, needles (from ethanol), m. p. 174° (Found: C, 75·6; H, 4·9. $C_{20}H_{15}O_3N$ requires C, 75·7; H, 4·7%). Both this acid and the non-crystalline ester were heated at temperatures between 200° and 300° but the desired diphenylamine was not obtained.

† p-*Formylphenyl* N-*phenylbenzimidate*.—This was prepared as above from benzanilide (24·6 g.) and *p*-hydroxybenzaldehyde (15·3 g.). The product crystallised after prolonged contact with alcohol, from which p-*formylphenyl* N-*phenylbenzimidate* (13·2 g.), prisms, m. p. 73° (Found: C, 79·7; H, 5·0. $C_{20}H_{15}O_3N$ requires C, 79·7; H, 5·0%), was obtained. In a similar way and in comparable yield m-*formylphenyl* N-*phenylbenzimidate* was obtained as needles, m. p. 84° (from ethanol) (Found: C, 79·7; H, 5·1%). Attempts to convert these substances into *N*-benzoylformyldiphenylamines by heat were unsuccessful. The *p*-formyl compound with aniline at 100° (3 hr.) gave an *anil*, needles, m. p. 118° (from ethanol) (Found: C, 82·8; H, 5·5. $C_{26}H_{20}ON_2$ requires C, 83·0; H, 5·3%), which rearranged at 270° (40 min.) giving N-*benzoyl*-4-*phenyliminoformyldiphenylamine*, prisms, m. p. 142° (from ethanol) (Found: C, 82·9; H, 5·3. $C_{26}H_{20}ON_2$ requires C, 83·0; H, 5·3%), which could not be successfully hydrolysed to give 4-formyldiphenylamine.

7-*Chloroformyl*-2 : 3-*diphenylindole*.—The acid (2·2 g.) with thionyl chloride (8 c.c.) was boiled in dry chloroform (40 c.c.) for 1½ hr. The solution was evaporated and the residue was recrystallised from light petroleum (b. p. 60—80°) from which 7-*chloroformyl*-2 : 3-*dimethylindole* separated as yellow prisms, m. p. 140—141° (Found: C, 75·9; H, 4·4. $C_{21}H_{14}ONCl$ requires C, 76·0; H, 4·2%). It gave an *amide*, prisms, m. p. 186—187° (from benzene) (Found: C, 80·4; H, 5·2. $C_{21}H_{16}ON_2$ requires C, 80·8; H, 5·1%), and an *anilide*, needles, m. p. 148—149° (from benzene) (Found: C, 83·8; H, 5·3. $C_{27}H_{20}ON_2$ requires C, 83·5; H, 5·2%).

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THE DYSON PERRINS LABORATORY, OXFORD. [*Received, November 25th*, 1957.]

† Experiments so marked were carried out, in part, by M. P. Lippner.

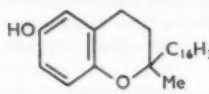
## 375. *Tocopherols. Part II.* Synthesis of Tocol*

By P. Mamalis, D. McHale, J. Green, and S. Marcinkiewicz.

A simple synthesis of tocol is described and details of a colorimetric assay are given.

For syntheses of 5- and 7-methyltocol (ε- and η-tocopherol) (cf. 16th Internat. Congr. Pure Appl. Chem., Paris, July, 1957), a quantity of tocol (I) was required. Pendse and Karrer [1] recently described a preparation of tocol by one-stage reaction from quinol with phytol, and this prompts us to record our own work.

Attempts to repeat the synthesis by Jacob *et al.*[2] showed that it was unsatisfactory. We found, however, that quinol monomethyl or monobenzyl ether reacted smoothly with phytol in formic acid–benzene, to give the tocol ethers in moderate yield. These were purified by distillation and their structures were confirmed by light-absorption data. Acid cleavage afforded tocol concentrates as pale yellow oils which were assayed by the chromatographic method of Green, Marcinkiewicz, and Watt.[3] Later experiments showed that protection of one of the hydroxyl groups was unnecessary, and tocol was prepared by direct condensation of phytol with quinol in benzene–formic acid: double chromans and phytyl-substituted tocols of the type postulated by Smith and Ungnade [4] were not readily formed as by-products in these condensations, suggesting that tocol is less reactive than the methylated tocols. As found in the preparation of other tocols by this route,[5] and contrary to the practice of Karrer and his co-workers,[6] it was unnecessary to treat the crude product with sodium methoxide in methanol before isolation. A 79% tocol concentrate, in 37% overall yield, was obtained by distillation of the crude product, from which the crystalline 3 : 5-dinitrophenylurethane and 4-phenylazobenzoate were readily prepared. Saponification of the latter derivative with potassium hydroxide in ethanol afforded pure tocol. The methyl and benzyl ethers were made from pure tocol and analytical and light-absorption data obtained.



(I)

Attempts to introduce a methyl or potential methyl group into the tocol molecule by (*a*) formaldehyde and hydrogen chloride in ether, (*b*) paraformaldehyde, hydrogen chloride, phosphoric and acetic acids, (*c*) formaldehyde and aqueous sodium hydroxide, and (*d*) dimethylformamide and phosphorus oxychloride, failed. Pendse and Karrer [1] also failed to convert tocol into formyltocol by the usual methods. These results confirm the lower reactivity of tocol than of the methylated homologues, which readily take part in reactions of this type.

The oxidation of tocol by ferric chloride in ethanol, in the presence of 2 : 2′-dipyridyl, was also different from the reaction of other tocopherols. The tocol samples were analysed colorimetrically by Eggitt and Ward's micro-procedure [7] as modified by Green *et al.*,[3] in which 20—100 μg. are oxidised by a large excess of ferric chloride in high concentration. This oxidation required about 80 minutes for completion, compared with 2 minutes (at most) for all the methylated tocols. This is no doubt related to the lack of nuclear reactivity,

* Part I, *J.*, 1958, 1600.

[1] Pendse and Karrer, *Helv. Chim. Acta*, 1957, **40**, 1837.
[2] Jacob, Sutcliffe, and Todd, *J.*, 1940, 327.
[3] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **6**, 274.
[4] Smith and Ungnade, *J. Org. Chem.*, 1939, **4**, 1298.
[5] Mamalis, Green, McHale, and Marcinkiewicz, unpublished work.
[6] Karrer and Fritzsche, *Helv. Chim. Acta*, 1938, **21**, 1234; 1939, **22**, 260; Karrer, Fritzsche, and Escher, *ibid.*, p. 661; Karrer, Koenig, Ringier, and Salomon, *ibid.*, p. 1139; Karrer and Leiser, *ibid.*, 1944, **27**, 678; Karrer and Kugler, *ibid.*, 1945, **28**, 436; Karrer and Dutta, 1948, **31**, 2080.
[7] Eggitt and Ward, *J. Sci. Food Agric.*, 1953, **4**, 176.

particularly at position 5, exemplified above. The diminished oxidation rate of the tocols, as nuclear methyl groups are removed, has already been noted by Stern and Baxter,[8] who found that 8-methyltocol (δ-tocopherol) only reacted completely, under their conditions, in 10 min., compared with 2·5 min. for 5 : 7 : 8-trimethyl-, 5 : 8-dimethyl- and 7 : 8-dimethyl-tocol (under our oxidation conditions, even 8-methyltocol reacts completely within 2 min.). The final stable spectrophotometric factor [7] of tocol is 75·2, identical with that found for 8-methyltocol in a 2 min. reaction; thus, in spite of the rate difference, both oxidations probably follow a similar course. The oxidation of 8-methyltocol has already been shown by Eggitt and Norris [9] to differ from that of more methylated tocols.

## Experimental

All tocol assays were carried out by the method of Green *et al.*,[3] with reaction for 100 min.

*Tocol Methyl Ether.*—Quinol monomethyl ether (2·93 g.), phytol (7·0 g.), dry benzene (50 ml.), and anhydrous formic acid (50 ml.) were heated under reflux for 4 hr. The benzene layer was separated, washed with N-sodium hydroxide and water, dried, and evaporated to give a straw-coloured oil (9·2 g.). Distillation afforded a pale yellow oil (5·1 g.), b. p. 195—205°/0·04 mm. This was redistilled in a micromolecular still, giving almost pure *tocol methyl ether*, b. p. 150° (bath)/$5 \times 10^{-4}$ mm. (Found: C, 80·0; H, 11·0. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%), $\lambda_{max.}$ 295 mμ ($E^{1\%}_{1\,cm.}$ 85·6), $\lambda_{min.}$ 255 mμ in EtOH.

*Tocol-3 : 5-dinitrophenylurethane from Tocol Methyl Ether.*—Tocol methyl ether (5·0 g.) was heated with hydrogen bromide in acetic acid (50 ml. of 43% w/v solution), acetic acid (50 ml.), and concentrated hydrochloric acid (10 ml.) for 6 hr. The cooled mixture was diluted with water and extracted with ether, the extracts were washed with saturated sodium hydrogen carbonate and water, then dried. Evaporation left a brown oil, which was distilled, giving a fraction (3·8 g.), b. p. 200—220°/0·1 mm (82% of tocol). This tocol concentrate (1·0 g.) in dry toluene (15 ml.) was heated with 3 : 5-dinitrobenzazide (0·83 g.) for 1 hr. After removal of solvent, the orange-red oil was diluted with light petroleum (10 ml.; b. p. 40—60°), and the insoluble dinitrophenylurea separated. The filtrate was again evaporated and the *dinitrophenylurethane* crystallised from aqueous ethanol as prismatic yellow needles (0·5 g.), m. p. 97° (Found: C, 66·3; H, 7·9; N, 6·9. $C_{33}H_{47}O_7N_3$ requires C, 66·3; H, 7·9; N, 7·0%).

*Tocol from Quinol Monobenzyl Ether.*—Quinol monobenzyl ether (1·0 g.), formic acid (10 ml.), and dry benzene (6 ml.) were heated under reflux while phytol (1·5 g.) in benzene (6 ml.) was added during 15 min., then the whole was heated further for 5½ hr. The benzene layer was separated, washed with N-sodium hydroxide followed by water, dried, and evaporated. Distillation of the resulting oil gave the benzyl ether concentrate as a yellow oil (2·0 g.), b. p. 190—200° (bath)/0·05 mm., which was shown by assay to contain a relatively large proportion of free tocol (27%) arising by fission of the ether. The distillate in ethanol (15 ml.) was shaken with hydrogen and 10% palladised charcoal till hydrogen uptake ceased (*ca.* 1 hr.), and the product isolated and distilled in a micromolecular still as a pale yellow oil (1·4 g.), b. p. 130—140° (bath)/$10^{-3}$ mm. (57% of tocol). This material was suitable for conversion into solid derivatives.

*Tocol from Quinol.*—Quinol (4·4 g.), phytol (11·8 g.), formic acid (60 ml.), and dry benzene (60 ml.) were heated on the steam-bath under nitrogen for 4 hr. The benzene layer was separated, the acid layer was extracted with benzene, and the combined benzene solutions were worked up in the usual way. Removal of the solvent left a light brown oil (13·6 g.), which was distilled, giving tocol concentrate (7·4 g.), b. p. 200—220°/0·05 mm. (assay, 79%; overall yield 37%). Paper chromatography showed the product to be free from other reducing material. A mixture of the concentrate (7·4 g.) and dry pyridine (11 ml.) in dry chloroform (50 ml.) was treated with 4-phenylazobenzoyl chloride (5·6 g.) in portions and heated on the steam-bath for 2 hr. Water (5 ml.) was added to the cooled mixture and after 5 minutes' shaking the product was taken up in light petroleum (b. p. 40—60°), and excess of 4-phenylazobenzoic acid was removed by filtration. The organic layer was washed with 2N-hydrochloric acid, then

[8] Stern and Baxter, *Analyt. Chem.*, 1947, **19**, 902.
[9] Eggitt and Norris, *J. Sci. Food Agric.*, 1956, **7**, 493.

water, and evaporated to yield a non-reducing red oil (11·2 g.). *Tocol 4-phenylazobenzoate* crystallised from aqueous propan-2-ol as orange needles which reddened on storage (5·0 g.), m. p. 35—37°. A further crystallisation raised the m. p. to 37—38° (Found: C, 77·9; H, 8·7; N, 4·4. $C_{39}H_{52}O_2N_2$ requires C, 78·4; H, 8·7; N, 4·7%). The combined crystallisation mother-liquors were concentrated, to give a semi-solid product which after saponification (see below) contained about 95% of tocol.

Crystalline tocol phenylazobenzoate (1·22 g.) in boiling ethanol (25 ml.) was treated with potassium hydroxide (1·2 g., added rapidly down the condenser) and heated for 30 min. To the refluxing solution, concentrated hydrochloric acid (3·5 ml.) was added, and the mixture cooled, treated with water (20 ml.) and light petroleum (b. p. 40—60°; 30 ml.), and filtered. The insoluble 4-phenylazobenzoic acid was rejected, and the organic layer washed with water, dried and evaporated to furnish a yellow oil (0·79 g.). Micromolecular distillation gave tocol as an almost colourless oil (0·69 g.), b. p. 130° (bath)/5 × $10^{-4}$ mm. (Found: C, 80·5; H, 11·5. Calc. for $C_{29}H_{44}O_2$: C, 80·4; H, 11·4%), $\lambda_{max.}$ 298·5 mμ ($E^{1\%}_{1cm.}$ 97), $\lambda_{min.}$ 255 mμ in EtOH, $\nu_{max.}$ 3375 s, 2915 vs, 1615 w, 1490 vs, 1450 vs, 1375 s, 1348 m, 1319 m, 1285 m, 1217 vs, 1152 s, 1106 m, 971 m, 930 m, 909 m, 883 m, 861 m, 811 m, 790 m cm.$^{-1}$ (liquid film).

*Tocol Ethers from Tocol.*—(a) *Tocol methyl ether.* Tocol (0·75 g.; regenerated from the phenylazobenzoate) in acetone (10 ml.) was treated successively with dimethyl sulphate (0·5 g.) and 30% aqueous sodium hydroxide (0·66 ml.), then shaken for 2 hr. at room temperature. Aqueous ammonia (1·0 ml.; *d* 0·880) was added, followed by water and light petroleum (b. p. 40—60°), the mixture separated, and the organic layer washed with water, dried, and evaporated. The residual oil was taken up in a small volume of 20 : 1 light petroleum (b. p. 40—60°)–benzene, and poured on a column of alumina (Peter Spence type " O," 6 × 1 cm.), and the methyl ether eluted with the same solvent mixture (100 ml.). Evaporation of the solvent yielded a pale yellow non-reducing oil (0·51 g.) which was distilled in a micromolecular still [b. p. 130—140° (bath)/5 × $10^{-4}$ mm.] as an almost colourless oil (Found: C, 80·8; H, 11·6. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%), $\lambda_{max.}$ 295 mμ ($E^{1\%}_{1cm.}$ 87·3), $\lambda_{min.}$ 259 mμ in EtOH, $\nu_{max.}$ 2890 vs, 1613 w, 1490 vs, 1460 s, 1430 m, 1375 m, 1319 m, 1299 m, 1269 n, 1218 m, 1099 s, 948 m, 896 m, 881 w, 858 w, 844 m, 813 m, 802 m cm.$^{-1}$ (liquid film).

(b) *Tocol benzyl ether.* Tocol (0·5 g.; regenerated from the phenylazobenzoate) in acetone (25 ml.) was shaken with benzyl bromide (0·90 ml.) and 4N-sodium hydroxide (1·8 ml.) at room temperature for 2 hr. The mixture was acidified with 2N-hydrochloric acid and extracted with light petroleum (b. p. 40—60°), and the extracts were washed with water. Distillation of the oil remaining after removal of solvent furnished *tocol benzyl ether* as a pale yellow viscous non-reducing oil, b. p. 150°(bath)/5 × $10^{-4}$ mm. (Found: C, 80·7, H, 11·0. $C_{33}H_{50}O_2$ requires C, 81·0; H, 10·5%), $\lambda_{max.}$ 296 mμ ($E^{1\%}_{1cm.}$ 88·5), $\lambda_{min.}$ 261 mμ in EtOH, $\nu_{max.}$ 3413 w, 2910 vs, 1720 w, 1610 w, 1500 vs, 1460 s, 1374 s, 1312 m, 1271 s, 1220, s, 1149 s, 1099 m, 1080 m, 1042 m, 1026 m, 948 w, 909 m, 885 w, 862 m, 842 m, 813 m, 779 w cm.$^{-1}$ (liquid film).

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## 376. *Pyridine-4-sulphonic Acid.*

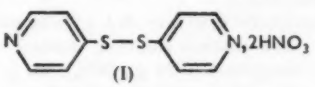
By A. M. Comrie and J. B. Stenlake.

The substance prepared by nitric acid oxidation of 4-thiopyridone and previously described as pyridine-4-sulphonic acid is shown to be a mixture of pyridine-4-sulphonic acid and di-4-pyridyl disulphide dinitrate. Pyridine-4-sulphonic acid can be prepared by oxidation of 4-thiopyridone with hydrogen peroxide in glacial acetic acid.

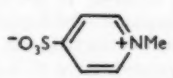
Koenigs and Kinne [1] oxidised 4-thiopyridone with nitric acid to an acid of m. p. 134—135° which they regarded as pyridine-4-sulphonic acid, and, in support of this structure, cited an analysis and preparation of a barium and a silver salt. King and Ware,[2] similarly, oxidised 4-thiopyridone, but with alkaline hydrogen peroxide, and obtained sodium pyridine-4-sulphonate. Neither from this salt nor from 4-thiopyridone could they prepare pyridine-4-sulphonyl chloride or the amide.

We have now oxidised 4-thiopyridone by hydrogen peroxide in glacial acetic acid and obtained an acid, $C_5H_5O_3NS$, of m. p. 333° which, as it was also prepared by passing a solution of sodium pyridine-4-sulphonate [2] through a cation-exchange resin, is undoubtedly pyridine-4-sulphonic acid. This was confirmed by potentiometric titration with sodium hydroxide (which gave a curve typical of that of a strong acid) and by analysis of the ammonium salt. Further, the high m. p. and the failure to form a picrate accord with the expected zwitterionic structure.

Repetition of Koenigs and Kinne's work [1] gave an acidic product of m. p. 135° which was separated by fractional crystallisation into pyridine-4-sulphonic acid, identical with that described above, and a larger proportion of a more soluble substance, m. p. 127°. The latter was readily soluble in water, giving a strongly acid solution, and titrated potentiometrically as a strong acid (equiv., 174). It was identified as di-4-pyridyl




(I)




(II)

disulphide dinitrate (I) by elementary analysis and by isolation of the corresponding base, identical with authentic material [2] (see below). The base picrate was identical (m. p. and crystal form) with di-4-pyridyl disulphide dipicrate. Preparation of the platinichloride [1] and oxidation with hydrogen peroxide in acetic acid to pyridine-4-sulphonic acid confirmed the identity of the base. The nitrate radical was established qualitatively (brown-ring test) and quantitatively (determination of the ammonia produced on reduction with Devarda's alloy).

The m. p. of the di-4-pyridyl disulphide has been variously reported as 155° [1] and 74°.[2] The material isolated as above from the dinitrate (I) melted at 74°. Disulphide prepared as described by Koenigs and Kinne [1] also melted at 74°. This with dilute nitric acid gave di-4-pyridyl disulphide dinitrate (I) identical with that obtained from 4-thiopyridone. Attempts to esterify pyridine-4-sulphonic acid by hydrogen chloride–ethanol,[3] trifluoroacetic anhydride–ethanol,[4] and dimethyl sulphate were unsuccessful. Treatment of the acid with diazomethane in presence of traces of water [5] gave the corresponding betaine (II), apparently identical (but with some discrepancy in m. p.) with that obtained by heating sodium pyridine-4-sulphonate with dimethyl sulphate.[6]

[1] Koenigs and Kinne, *Ber.*, 1921, **54**, 1357.
[2] King and Ware, *J.*, 1939, 873.
[3] U.S.P. 2,349,060 (1944).
[4] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976.
[5] Biltz, *Ber.*, 1922, **55**, 1066.
[6] Larivé, Collet, and Dennilauber, *Bull. Soc. chim. France*, 1956, 1443.

## Experimental

4-Thiopyridone was prepared from chelidonic acid [7] as described by King and Ware.[2]

*Pyridine-4-sulphonic Acid.*—(*a*) 4-Thiopyridone (0·5 g.), in glacial acetic acid (10 ml.) and 30% hydrogen peroxide (1·6 ml.), was heated on a water-bath for ½ hr. Acetic acid was removed under reduced pressure. The residue recrystallised from aqueous methanol (charcoal) in colourless plates (0·25 g., 36%) of *pyridine-4-sulphonic acid*, m. p. 333° (decomp.) [Found: C, 37·5; H, 3·0; N, 8·8%; equiv. (potentiometric titration), 160. $C_5H_5O_3NS$ requires C, 37·7; H, 3·1; N, 8·8%; equiv., 159].

(*b*) Sodium pyridine-4-sulphonate, prepared as described by King and Ware,[2] was dissolved in water, and the solution passed through a column of Zeo-Karb 225. The eluate, evaporated to dryness, gave pyridine-4-sulphonic acid, m. p. 333—334° (decomp.) (from ethanol–water), identical with that obtained as in method (*a*). The *ammonium salt* separated from aqueous methanol at 0° as a colourless solid, m. p. 256° (decomp.) (Found: N, 16·2. $C_5H_8O_3N_2S$ requires N, 15·9%).

(*c*) Di-4-pyridyl disulphide (0·5 g.), treated as in (*a*) for the acid, yielded pyridine-4-sulphonic acid, m. p. 333° (from aqueous methanol), identical with that obtained as in method (*a*).

*Oxidation of 4-Thiopyridone with Nitric Acid.*—4-Thiopyridone (2 g.) was heated on a water-bath with nitric acid (*d* 1·2; 20 ml.) until vigorous reaction commenced (*ca.* 5 min.). After the reaction had subsided the solution was evaporated to dryness. The residue (3·3 g.), recrystallised from water (8 ml.), gave pale yellow needles of *di-4-pyridyl disulphide dinitrate* (1·8 g., 58%) which, after being washed with ice-cold water (2 ml.) and dried *in vacuo*, had m. p. 127° (decomp.) [Found: C, 35·0; H, 2·5: N, 15·8; Nitrate-N (determined by reduction with Devarda's alloy in a Conway cell and titration of the liberated ammonia), 8·0, 8·2. $C_{10}H_{10}O_6N_4S_2$ requires C, 34·7; H, 2·9; N, 16·2; Nitrate-N, 8·1%].

The combined mother-liquors and washings, treated with ethanol (40 ml.), deposited a crystalline solid, m. p. 135° (decomp.) (1·1 g.); recrystallisation from aqueous ethanol gave colourless plates of pyridine-4-sulphonic acid (0·53 g.), m. p. 333—334° (decomp.), identical with authentic material. The filtrate was evaporated to dryness and the residue recrystallised from 90% ethanol (22 ml.), affording a further yield of pyridine-4-sulphonic acid (0·41 g.) (total yield 27%) (Found: C, 37·6; H, 3·0%; equiv., 158).

*Di-4-pyridyl Disulphide.*—Di-4-pyridyl disulphide dinitrate (0·4 g.) was treated with dilute aqueous ammonia and extracted with ether. The ethereal solution, washed with water, dried ($Na_2SO_4$), and evaporated, gave di-4-pyridyl disulphide (0·26 g., 96%), m. p. 75—76°. King and Ware [1] gave m. p. 74—75°. Disulphide prepared by oxidation of 4-thiopyridone in sodium hydroxide as described by Koenigs and Kinne [1] had m. p. 74—75° (Found: C, 54·4; H, 3·4. Calc. for $C_{10}H_8N_2S_2$: C, 54·5; H, 3·7%). The dipicrate (from methanol) had m. p. 230° (decomp.) (lit.,[2] m. p. 231°) (Found: C, 39·2; H, 1·9; S, 9·6. Calc. for $C_{22}H_{14}O_{14}N_8S_2$ requires C, 38·9; H, 2·1; S, 9·4%). The platinichloride formed golden-yellow plates, which decomposed about 285° (Koenigs and Kinne [1] report decomposition without melting at 275°) (Found: C, 18·7; H, 1·6; Pt, 31·0. Calc. for $C_{10}H_{10}N_2Cl_6S_2Pt$: C, 19·1; H, 1·6; Pt, 30·95%).

*N-Methyl-4-sulphopyridine Betaine.*—Pyridine-4-sulphonic acid (0·32 g.) was suspended in ether (10 ml.) and treated with excess of diazomethane. A few drops of water were added as catalyst. The reddish-brown precipitate, recrystallised from aqueous ethanol, gave the betaine (0·19 g., 54%) as colourless crystals, decomp. 330° (Found: C, 41·6; H, 3·6; N, 7·8. Calc. for $C_6H_7O_3NS$: C, 41·6; H, 4·1; N, 8·1%). Larivé *et al.*[6] report decomposition at 340° and 345°.

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The School of Pharmacy, The Royal College of Science and Technology, Glasgow. [*Received, November 14th*, 1957.]

[7] *Org. Synth.*, 1937, **17**, 40.

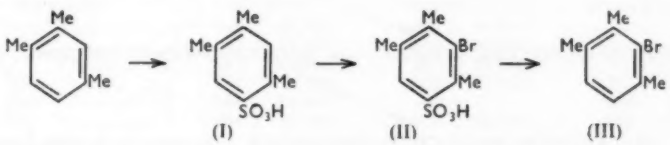
## 377. *Studies in the Polyene Series. Part LIII.* The Synthesis of* pseudo*Cumyl Analogues of* β-*Ionone and Vitamin A Acid.*

By G. Lowe, F. G. Torto, and B. C. L. Weedon.

4-(2 : 3 : 6-Trimethylphenyl)but-3-en-2-one, a metabolic product of pregnant mares, has been synthesised by a convenient route and used in a preparation of a biologically active *pseudo*cumyl analogue of vitamin A acid.

The synthesis of three aryl analogues, phenyl, *o*-tolyl, and mesityl, of vitamin A acid has already been reported.[1,2] Of these, only the mesityl compound exhibited growth-promoting activity. It is perhaps significant that this is also the only one for which spectral data indicated a non-planar structure similar to that of vitamin A itself. In continuation of these studies on structure, light-absorption properties, and biological activity, we have prepared the 3-*pseudo*cumyl analogue because the alkyl substitution in both *ortho*-positions was expected to result again in a non-planar structure; furthermore this ring system is encountered in metabolic products which are believed to be of carotenoid origin.[3]

An obvious key intermediate was the β-ionone analogue (V) which occurs naturally in the urine of pregnant mares[3] and has been synthesised on a small scale both from *pseudo*cumene[4] and from β-ionone.[5] To avoid the risk of contamination with β-ionone, which might lead to traces of vitamin A acid in the final product and thus invalidate the biological assay, attention was directed to the former route. In this the first stage is conversion of *pseudo*cumene into 3-bromo*pseudo*cumene after blocking of the more reactive 5-position.




Sulphonation of *pseudo*cumene by the method of Smith and Cass[6] gave the 5-sulphonic acid (I) almost quantitatively. Smith and Moyle[7] described a bromination of the sodium salt of this acid in ethanol–chloroform which gave 3-bromo*pseudo*cumene-5-sulphonic acid (II) exclusively, but Smith and Kiess[8] reported that the reaction was not repeatable. However, they claimed that bromination of the sulphonic acid in 1 : 1 hydrochloric acid gave a readily separable mixture of 5-bromo*pseudo*cumene (60%) and the 3-bromo*pseudo*-cumene-5-sulphonic acid; the latter on hydrolysis with sulphuric acid furnished 3-bromo-*pseudo*cumene (III) in 6% overall yield. Our attempts to reproduce the experimental conditions described by Smith and Kiess were unsuccessful, the starting acid being insoluble in the medium recommended. Various brominations in hydrochloric acid media were therefore examined (see p. 1858), but the yield of 3-bromo*pseudo*cumene, after hydrolysis of the initial bromo-sulphonic acid, did not exceed 9%, the main product being either 5-bromo*pseudo*cumene formed by replacement of the sulphonic acid grouping during

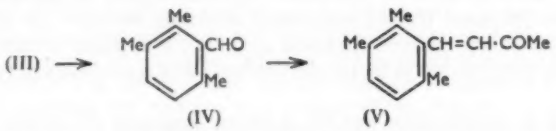
* Part LII, *J.*, 1957, 4909.

[1] Weedon and Woods, *J.*, 1951, 2687.
[2] Bharucha and Weedon, *J.*, 1953, 1571.
[3] Prelog, Führer, Hagenbach, and Schneider, *Helv. Chim. Acta*, 1948, **31**, 1799.
[4] Prelog, Führer, Hagenbach, and Frick, *ibid.*, 1947, **30**, 113.
[5] Braude, Jackman, Linstead, and Lowe, unpublished results; cf. Karrer and Ochsner, *Helv. Chim. Acta*, 1948, **31**, 2093; Büchi, Seitz, and Jeger, *ibid.*, 1949, **32**, 39.
[6] Smith and Cass, *J. Amer. Chem. Soc.*, 1932, **54**, 1603.
[7] Smith and Moyle, *ibid.*, 1936, **58**, 1.
[8] Smith and Kiess, *ibid.*, 1939, **61**, 284.

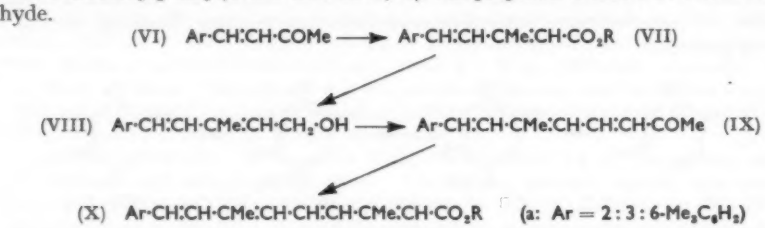
the bromination, or tribromo*pseudo*cumene by further substitution. Our attempts to effect a Jacobsen rearrangement of the 5-bromo- to the 3-bromo-*pseudo*cumene by both the procedures reported [7,9] were unsuccessful.

In the belief that the formation of 5-bromo- and tribromo-*pseudo*cumene in the above reactions was associated with the ease of hydrolysis of *pseudo*cumene-5-sulphonic acid in aqueous media, the bromination was repeated in concentrated sulphuric acid. This gave a readily separable mixture of tribromo*pseudo*cumene (9%) and 3-bromo*pseudo*cumene-5-sulphonic acid. The latter was hydrolysed directly and furnished 3-bromo-*pseudo*cumene in *ca.* 80% overall yield from *pseudo*cumene.

Reaction of the Grignard reagent from 3-bromo*pseudo*cumene with ethyl orthoformate, and hydrolysis of the product, provided 2 : 3 : 6-trimethylbenzaldehyde (IV) in 77% yield. Condensation with acetone in the presence of sodium hydroxide then gave (60%) the required ionone analogue (V) which was characterised by a number of crystalline derivatives.




Its properties, and those of its phenylsemicarbazone, agree well with those reported for the specimens of natural origin.[3,4] In connection with the spectral studies, the isomeric 4-(2 : 4 : 5-trimethylphenyl)but-2-en-2-one (VI) was prepared from 2 : 4 : 5-trimethylbenzaldehyde.


(VI) Ar·CH:CH·COMe → Ar·CH:CH·CMe:CH·CO₂R (VII)
(VIII) Ar·CH:CH·CMe:CH·CH₂·OH → Ar·CH:CH·CMe:CH·CH:CH·COMe (IX)
(X) Ar·CH:CH·CMe:CH·CH:CH·CMe:CH·CO₂R (a: Ar = 2 : 3 : 6-Me₃C₆H₂)

A Reformatsky reaction of the ketone (V = VIa) with ethyl bromoacetate, and dehydration of the initial product, yielded the ester (VIIa), which was reduced with lithium aluminium hydride to the alcohol (VIIIa). Oxidation with acetone and aluminium *tert.*-butoxide then gave the ketone (IXa) directly by condensation of the aldehyde first formed with excess of acetone. A Reformatsky reaction of this ketone with methyl bromoacetate led to the acid (Xa; R = H) which was converted by diazomethane into the crystalline methyl ester (Xa; R = Me).

The crystalline ester was fed in arachis oil to young rats reared on a diet free from vitamin A, in doses intended to reveal potency of the same order as that of the mesityl analogue. Under these conditions the rats grew normally. The *pseudo*cumyl ester must therefore possess at least 0·2% of the growth-promoting activity of vitamin A. Further biological assays, designed to determine the upper limit of activity, will be carried out when material is available.

Spectral properties of many of the compounds mentioned above are summarised in the accompanying Tables. The data for the trimethylbenzaldehydes (Table 1) and the derived ionone analogues (Table 2) supplement previous results on the influence of alkyl substitution in the benzaldehyde and benzylideneacetone series.[2,10,11] 2 : 3 : 6-Trimethylbenzaldehyde, like 2 : 6-dimethylbenzaldehyde, exhibits absorption at a longer

[9] Smith, *Organic Reactions*, 1942, **1**, 370.
[10] Braude and Sondheimer, *J.*, 1955, 3754.
[11] *Idem, ibid.*, p. 3773.

wavelength than benzaldehyde, but of appreciably lower intensity. These bathochromic shifts are doubtless due to the increased alkyl substitution, whilst the hypochromic shifts may be explained in terms of steric interference between the *o*-methyl groups and the formyl group. The greater drop in intensity for the 2 : 3 : 6-trimethyl than for the 2 : 6-dimethyl compound is interesting, and indicates that the steric effect of an *o*-methyl group is enhanced by a further methyl group on the adjacent (*i.e.*, *meta*-)position. This " buttressing " effect is even more evident in the spectra of the corresponding semicarbazone and 2 : 4-dinitrophenylhydrazone, and in those of the benzylideneacetone and its derivatives.

TABLE 1. *Ultraviolet-light absorption* ($\lambda_{max.}$, *followed by* $\varepsilon$) *of alkylated benzaldehydes and their derivatives.*

| Ph·CHO derivative | Aldehyde | | Semicarbazone [a] | | 2 : 4-Dinitrophenylhydrazone [b] | |
|---|---|---|---|---|---|---|
| Unsubstd. [c] | 242 [d] | 14,000 | 281 | 22,000 | — | — |
| | 248 | 12,500 | | | | |
| 2-Me [c] | 243 | 12,500 | 281 | 17,700 | 386 | 30,600 |
| | 251 | 13,000 | 291 | 17,300 | | |
| 2 : 6-$Me_2$ [c] | 251 [d] | 12,500 | 281 | 17,600 | 380 | 30,800 |
| | 256 | 11,500 | 291 | 16,200 | | |
| 2 : 3 : 6-$Me_3$ | 256 [e] | 8,000 | 268 [e] | 13,000 | 376 | 30,000 |
| | | | 280 | 14,500 | | |
| 2 : 4 : 6-$Me_3$ [c] | 264 [d] | 14,500 | 281 | 18,500 | 386 | 29,500 |
| | | | 290 | 17,800 | | |
| 2 : 4 : 5-$Me_3$ | 262 [e] | 13,000 | 286 | 22,000 | 386 | 27,000 |

TABLE 2. *Ultraviolet-light absorption* ($\lambda_{max.}$, *followed by* $\varepsilon$) *of alkylated benzylideneacetones (arylbut-3-en-2-ones) and their derivatives.*

| Ph·CH:CH·CO·Me derivative | Ketone [a] | | Semicarbazone [a] | | 2 : 4-Dinitrophenylhydrazone [b] | |
|---|---|---|---|---|---|---|
| Unsubstd. [c] | 286 | 22,200 | 305 | 38,600 | — | — |
| 2-Me [c,f] | 290 | 17,000 | 304 | 32,500 | — | — |
| 2 : 6-$Me_2$ [c] | 291 | 10,500 | 282 | 23,300 | — | — |
| 2 : 3 : 6-$Me_3$ | 284 | 9,400 | 280 | 21,000 | 384 | 29,000 |
| 2 : 4 : 6-$Me_3$ [f] | 293 | 14,000 | — | — | 394 | 23,000 |
| 2 : 4 : 5-$Me_3$ | 304 | 16,000 | 310 | 28,500 | 395 | 33,000 |

TABLE 3. *Ultraviolet-light absorption* ($\lambda_{max.}$, *followed by* $\varepsilon$) *of phenylpolyene derivatives.*

| Ar | Diene acid (VII; R = H) | | Triene ketone (IX) | | Tetraene ester (X; R = Me) | |
|---|---|---|---|---|---|---|
| $C_6H_5$ [g] | 229 | 13,500 | 360 | 42,000 | 354 [a] | 44,500 |
| | 309 | 28,000 | | | 367 | 48,500 |
| 2-Me·$C_6H_4$ [f] | 227 [h] | 10,500 | 360 | 42,500 | 369 | 52,000 |
| | 307 | 27,500 | | | | |
| | 312 [a] | 24,000 | | | | |
| 2 : 3 : 6-$Me_3C_6H_2$ | 292 | 13,800 | 343 | 24,000 | 352 | 37,800 |
| 2 : 4 : 6-$Me_3C_6H_2$ [f] | 227 | 10,500 | 348 | 28,000 | 358 | 37,500 |
| | 290 [a] | 14,000 | | | | |
| | 304 | 16,000 | | | | |
| | 312 [a] | 14,000 | | | | |

*Footnotes to all Tables*:
[a] Inflexion. [b] In alcohol. [c] In chloroform. [d] Braude and Sondheimer, *J.*, 1955, 3754. [e] In *n*-hexane or *cyclo*hexane. [f] Braude and Sondheimer, *J.*, 1955, 3773. Bharucha and Weedon, *J.*, 1953, 1571. [g] Weedon and Woods, *J.*, 1951, 2687. [h] Ethyl ester.

These 2 : 3 : 6-trimethyl compounds exhibit maximal absorption at slightly lower wavelengths, as well as of lower intensity, than either the 2 : 6-dimethyl or the unmethylated compounds. The spectra of the 2 : 4 : 5-trimethyl compounds show the normal bathochromic shifts due to the methyl substitution, the presence of only one *o*-methyl group giving rise to comparatively little steric hindrance, as was noted previously in the *o*-tolyl series.[2]

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With the 3-*pseudo*cumyl polyenes (Table 3) strong hypsochromic and hypochromic effects are observed. These, like those in the mesityl series,[2] are attributed to steric inhibition of resonance, the unsaturated side-chain being displaced out of the plane of the benzene ring by the *o*-methyl groups.

## Experimental

See notes preceding the Experimental section in Part XLVI.[3] M. p.s marked (K) were determined on a Kofler block and are corrected.

3-*Bromo*pseudo*cumene* (III).—Concentrated sulphuric acid (700 c.c.) was added slowly to vigorously stirred *pseudo*cumene (300 g.). After the temperature of the mixture had fallen to 20°, bromine (450 g.) was added during 2 hr. Hydrogen bromide was evolved and a solid separated. When all the bromine had reacted water (700 c.c.) was added and the mixture was cooled. The solid, a mixture of tribromo*pseudo*cumene and 3-bromo*pseudo*cumene-5-sulphonic acid, was separated and extracted with hot water. The water-insoluble fraction (80 g.), m. p. 228—232°, was filtered off and crystallised from aqueous methanol, giving tribromo*pseudo*cumene as colourless needles, m. p. 232° (Smith and Moyle [7] give m. p. 231·5°). The aqueous solution of the bromo-sulphonic acid was concentrated and then added slowly to hot (*ca.* 175—180°) 80% (w/w) sulphuric acid through which steam was passed. Isolation of the product from the steam-distillate and distillation gave a liquid (416 g., 84%), b. p. 111—118°/5 mm., $n_D^{23}$ 1·5555. Redistillation gave 3-bromo*pseudo*cumene (342 g., 69%), b. p. 111—114°/5 mm., $n_D^{23}$ 1·5550 (Smith and Kiess [8] give b. p. 85·5—86·5°/5 mm., $n_D^{20}$ 1·5575).

*Bromination of* pseudo*Cumene-5-sulphonic Acid.*—(a) *In cold hydrochloric acid.* A mixture of bromine (500 g.), water (112 c.c.), and concentrated hydrochloric acid (112 c.c.) was added during 24 hr. to a stirred suspension of *pseudo*cumene-5-sulphonic acid (from 360 g. of *pseudo*cumene [6]) in water (225 c.c.) and concentrated hydrochloric acid (225 c.c.). The solid (440 g.), m. p. 60—90°, was filtered off; steam-distillation and crystallisation from aqueous methanol gave 5-bromo*pseudo*cumene as plates, m. p. 72° (Smith and Moyle [7] give m. p. 71·5—72·5°). The aqueous filtrate of bromo-sulphonic acid was processed as described above and gave 3-bromo*pseudo*cumene (12 g., 2%), b. p. 78—79°/1 mm.

Bromination of the sulphonic acid (from 20 g. of *pseudo*cumene) in N-hydrochloric acid gave 3-bromo*pseudo*cumene in 9% yield.

(b) *In hot hydrochloric acid.* A mixture of bromine (165 g.), water (38 c.c.) and concentrated hydrochloric acid (38 c.c.) was added slowly to a warm saturated solution of *pseudo*cumene-5-sulphonic acid (from 120 g. of *pseudo*cumene) in water (75 c.c.) and concentrated hydrochloric acid (75 c.c.). The solid (110 g.), m. p. 180—200°, which separated was collected; from it 5-bromo*pseudo*cumene (9 g.), m. p. 71°, was isolated by steam-distillation, and tribromo-*pseudo*cumene, m. p. 232°, by crystallisation from aqueous methanol. The aqueous filtrate of bromosulphonic acid was processed in the usual way and gave 3-bromo*pseudo*cumene (16 g., 7·7%), b. p. 77—78°/0·8 mm.

(c) *In organic solvents.* Addition of bromine (28 g.) in chloroform (11 c.c.) and concentrated hydrochloric acid (1 c.c.) to a solution of the sulphonic acid (from 20 g. of *pseudo*cumene) in alcohol (35 c.c.) and concentrated hydrochloric acid (15 c.c.), and hydrolysis of the resulting bromo-sulphonic acid, gave 3-bromo*pseudo*cumene (2·9 g., 9%).

Bromination of the sulphonic acid (from 20 g. of *pseudo*cumene) in acetic acid (50 c.c.) and water (20 c.c.) with bromine (28 g.) in acetic acid (12 c.c.), and treatment of the product in the usual way, gave a negligible yield of 3-bromo*pseudo*cumene.

2 : 3 : 6-*Trimethylbenzaldehyde* (IV).—3-Bromo*pseudo*cumene (50 g.) in ether (80 c.c.) was added to a stirred suspension of magnesium turnings (13·3 g.) in ether (35 c.c.) containing a trace of iodine. Ethyl bromide (27 g.) in ether (150 c.c.) was added slowly and the mixture then boiled under reflux for 3 hr. during which most of the magnesium reacted. Ethyl orthoformate (77 g.) in ether (50 c.c.) was added and the mixture was boiled for 5 hr. The ether was then distilled off and the residue was kept at 20° overnight. Ice (80 g.) and 5N-hydrochloric acid (200 c.c.) were added. The mixture was boiled under reflux for 30 min. in an atmosphere of carbon dioxide and then steam-distilled. Extraction of the product from the distillate with ether and distillation gave 2 : 3 : 6-trimethylbenzaldehyde (28·5 g.), b. p. 74°/1 mm., $n_D^{26}$ 1·5430 (Smith and Nichols [12] give b. p. 115—116°/12 mm.). Light absorption: see Table 1. The

semicarbazone crystallised from aqueous alcohol and had m. p. 166—167° (lit.,[12] m. p. 167—169°). Light absorption: see Table 1. The oxime, after vacuum-sublimation and crystallisation from aqueous alcohol, had m. p. 138° (lit.,[12] m. p. 124—126°) (Found: C, 73·85; H, 8·55. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 8·05%). The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid or ethyl acetate in red prisms, m. p. 222—223° (corr.) (Found: C, 59·05; H, 4·95; N, 17·05. $C_{16}H_{16}O_4N_4$ requires C, 58·55; H, 4·9; N, 17·05%). Light absorption: see Table 1.

The use of activated magnesium powder in the Grignard reaction, as advocated by Smith and Nichols,[12] was found unnecessary.

2 : 4 : 5-*Trimethylbenzaldehyde*.—Hydrogen cyanide (48 c.c.) was added during 15 min. to a stirred suspension of aluminium chloride (107 g.) in tetrachloroethane (200 c.c.) at 0°. After the mixture had been stirred at 20° for 15 min., *pseudo*cumene (25 g.) was added and a slow stream of dry hydrogen chloride was bubbled through the mixture for 15 min. at 20° and then for 4 hr. at 80°. The product was cooled and poured on ice and concentrated hydrochloric acid. This mixture was boiled for 15 min. under reflux and then steam-distilled. Extraction of the distillate with ether, and distillation, gave a liquid which partly solidified at 8°. The solid was collected and crystallised from aqueous alcohol, to give 2 : 4 : 5-trimethylbenzaldehyde (2·0 g.) as prisms, m. p. 45°, undepressed on admixture with a specimen prepared according to Smith and Nichols's method [12] (Gattermann [13] gives m. p. 42°). Light absorption: see Table 1. The 2 : 4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid or ethyl acetate in orange prisms, m. p. 223° (corr.) (Found: C, 58·75; H, 5·25; N, 17·15%). Light absorption: see Table 1. A mixed m. p. with the derivative of 2 : 3 : 6-trimethylbenzaldehyde showed a marked depression. The *semicarbazone* crystallised from methanol–chloroform and had m. p. 244° (Found: C, 64·11; H, 7·35. $C_{11}H_{15}ON_3$ requires C, 64·35; H, 7·35%). Light absorption: see Table 1. The oxime crystallised from aqueous alcohol and had m. p. 112° (Gattermann [13] gives m. p. 102°) (Found: C, 73·9; H, 8·2%), $\lambda_{max.}$ 262 mμ (ε 15,500).

A higher yield of 2 : 4 : 5-trimethylbenzaldehyde is obtained by the original method of Gattermann.[13]

4-(2 : 3 : 6-*Trimethylphenyl*)*but*-3-*en*-2-*one*.—Sodium hydroxide (2·5 g.) was added to a solution of 2 : 3 : 6-trimethylbenzaldehyde (27·4 g.) in acetone (142 c.c.) and water (14·5 c.c.). The mixture was stirred at 20° for 20 hr., then poured into 2N-sulphuric acid (290 c.c.). A solid (1·2 g.) was filtered off and crystallised from ethyl acetate, to give 1 : 5-*di*-(2 : 3 : 6-*trimethylphenyl*)*penta*-1 : 4-*dien*-3-*one* as yellow needles, m. p. 152° (Found: C, 86·4; H, 8·4. $C_{23}H_{26}O$ requires C, 86·75; H, 8·25%), $\lambda_{max.}$ 314 mμ (ε 17,000).

The aqueous-acetone filtrate was extracted with ether, and the extract was washed with water, dried, and evaporated. Distillation of the residue gave 4-(2 : 3 : 6-trimethylphenyl)-but-3-en-2-one (21 g.), b. p. 97°/0·1 mm., $n_D^{19}$ 1·5632 (Found: C, 82·6; H, 8·65. Calc. for $C_{13}H_{16}O$: C, 82·9; H, 8·55%). Light absorption: see Table 2. (Prelog, Führer, Hagenbach, and Frick [4] give b. p. 115—130°/0·2 mm.). The semicarbazone crystallised from alcohol and had m. p. 215° (lit.,[4] m. p. 216—217°). Light absorption: see Table 2. The phenylsemicarbazone crystallised from alcohol in needles, m. p. 203—205° (lit.,[4] m. p. 202—204°) (Found: C, 74·8; H, 7·25; N, 13·35. Calc. for $C_{20}H_{23}ON_3$: C, 74·75; H, 7·2; N, 13·05%), $\lambda_{max.}$ 228 and 292 mμ (ε 23,000 and 32,000 respectively). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in needles, m. p. 154° (Found: C, 61·85; H, 5·65. $C_{19}H_{20}O_4N_4$ requires C, 61·95; H, 5·45%). Light absorption: see Table 2. The *oxime*, which was formed slowly, crystallised from aqueous alcohol and had m. p. 106° (Found: C, 76·35; H, 8·5. $C_{13}H_{17}ON$ requires C, 76·8; H, 8·45%), $\lambda_{max.}$ 266 mμ (ε 15,000).

4-(2 : 4 : 5-*Trimethylphenyl*)*but*-3-*en*-2-*one*.—Sodium hydroxide (0·154 g.) was added to a solution of 2 : 4 : 5-trimethylbenzaldehyde (1·67 g.) in acetone (7·8 c.c.) and water (0·88 c.c.). The mixture was stirred at 20° overnight and then poured into 2N-sulphuric acid (18 c.c.). The product was isolated by extraction with ether. Crystallisation from aqueous methanol and from *n*-pentane gave the ketone (1·0 g., 47%) as needles, m. p. 45° (John and Gunther [14] give m. p. 51°) (Found: C, 82·9; H, 8·85%). Light absorption: see Table 2. The semicarbazone crystallised from chloroform and had m. p. 222° (decomp.) [lit.,[14] m. p. 220° (decomp.)]. Light absorption: see Table 2. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in

[12] Smith and Nichols, *J. Org. Chem.*, 1941, **6**, 489.
[13] Gattermann, *Annalen*, 1906, **347**, 347.
[14] John and Gunther, *Ber.*, 1941, **74**, 879.

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needles, m. p. 240° (Found: C, 61·5; H, 5·5%). Light absorption: see Table 2. The *oxime* crystallised from aqueous methanol and had m. p. 140° (decomp.) (Found: C, 76·3; H, 8·7%), $\lambda_{max.}$ 288 mμ (ε 21,000).

*Ethyl 2-Methyl-4-(2 : 3 : 6-trimethylphenyl)buta-1 : 3-diene-1-carboxylate* (VII; R = Et).—About half of a mixture of 4-(2 : 3 : 6-trimethylphenyl)but-3-en-2-one (31·2 g.) and ethyl bromoacetate (31·2 g.) was added to zinc wool (12·5 g.) and benzene (110 c.c.). The mixture was heated under reflux until reaction commenced, and the remainder of the ketone-ester mixture was then added at such a rate that gentle refluxing was maintained. Heating was then recommenced and continued for ½ hr. The mixture was cooled and shaken with N-acetic acid (1 l.). The benzene layer was separated, washed with saturated sodium hydrogen carbonate solution, and dried ($Na_2SO_4$). The solution was diluted (to 500 c.c.) with the same solvent and heated under reflux for 5 hr. with toluene-*p*-sulphonic acid (0·5 g.), water being removed by azeotropic distillation. The resulting benzene solution was washed with aqueous sodium hydrogen carbonate, dried and evaporated. Distillation gave the *ester* (35·5 g.), b. p. 85—95° (bath temp.)/$10^{-5}$ mm., $n_D^{21}$ 1·5750 (Found: C, 79·25; H, 8·75. $C_{17}H_{22}O_2$ requires C, 79·05; H, 8·6%), $\lambda_{max.}$ 294 mμ (ε 19,000).

*2-Methyl-4-(2 : 3 : 6-trimethylphenyl)buta-1 : 3-diene-1-carboxylic Acid* (VII; R = H).—Hydrolysis of the preceding ester (740 mg.) with boiling methanolic 10% (w/v) potassium hydroxide (15 c.c.) for 3 hr., and isolation of the acidic product in the usual way, gave a solid (500 mg.), m. p. 134—170°. Fractional crystallisation from benzene–light petroleum (b. p. 60—80°) yielded one stereoisomer of the *acid* (200 mg.), m. p. (K) 172—174° (Found: C, 78·2; H, 8·0. $C_{14}H_{18}O_2$ requires C, 78·25; H, 7·9%). Light absorption: see Table 3.

*3-Methyl-4-(2 : 3 : 6-trimethylphenyl)penta-2 : 4-dien-1-ol* (VIII).—The above ester (40·8 g.) in ether (175 c.c.) was added during 3 hr. to a stirred solution of lithium aluminium hydride (8 g.) in ether (200 c.c.) at −60°. The mixture was then stirred for 1½ hr. at −30°. Ethyl acetate (10 c.c.) was added to decompose any excess of hydride, and then a saturated solution of ammonium chloride (50 c.c.). The mixture was filtered and the product was isolated in the usual way, giving the *alcohol* (28·0 g.), b. p. 95—115° (bath-temp.)/$10^{-5}$ mm., $n_D^{19}$ 1·5816 (Found: C, 83·15; H, 9·6. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%), $\lambda_{max.}$ 223 and 267 mμ (ε 19,500 and 16,000 respectively).

A small portion (0·7 g.) of the alcohol in light petroleum (b. p. 40—60°) (30 c.c.) was shaken with manganese dioxide (3·5 g.) at 20° for 96 hr. Removal of oxide and solvent, and distillation of the residue, gave an impure aldehyde (0·2 g.), b. p. 100—110° (bath-temp.)/$10^{-5}$ mm., $n_D^{21}$ 1·6090 (Found: C, 83·95; H, 8·75. $C_{15}H_{18}O$ requires C, 84·05; H, 8·45%), $\lambda_{max.}$ 258, 268, and 280 mμ ($E_{1cm.}^{1\%}$ 620). The *semicarbazone* crystallised from ethanol and had m. p. (K) 176° (Found: N, 15·6. $C_{16}H_{21}ON_3$ requires N, 15·5%), $\lambda_{max.}$ 320 mμ (ε 40,000).

*6-Methyl-8-(2 : 3 : 6-trimethylphenyl)octa-3 : 5 : 7-trien-2-one* (IX).—The preceding alcohol (21·8 g.) and aluminium *tert.*-butoxide (37 g.) in acetone (185 c.c.) and benzene (500 c.c.) were heated under reflux for 46 hr. The mixture was cooled and shaken with 2N-sulphuric acid. The benzene layer was separated, washed with aqueous sodium hydrogen carbonate, dried ($Na_2SO_4$), and evaporated under reduced pressure. A solution of the residual oil (27·5 g., $n_D^{21}$ 1·663) and Girard reagent T [15] (20 g.) in alcohol (225 c.c.) and glacial acetic acid (18 g.) was heated under reflux for 1 hr. and then cooled. Ice and water (1700 c.c.) were added, and the mixture was brought to pH 6 by the addition of 2N-sodium hydroxide. The non-ketonic fraction was extracted with ether. 2N-Sulphuric acid (600 c.c.) was added to the aqueous layer and, after the mixture had been kept for 1 hr., the liberated ketone was isolated with ether in the usual way, giving an oil (12·3 g.), $n_D^{22}$ 1·644. This crude product was treated with excess of methanolic semicarbazide acetate and gave a solid (16·9 g.), m. p. 171—177°. Crystallisation from alcohol yielded the *semicarbazone* as yellow needles, m. p. (K) 181—182° (Found: N, 13·55. $C_{19}H_{25}ON_3$ requires N, 13·5%), $\lambda_{max.}$ 339 mμ (ε 62,000).

A mixture of the finely powdered semicarbazone (8·3 g.; m. p. 176—181°), 2N-sulphuric acid (170 c.c.), and light petroleum (b. p. 100—120°) (120 c.c.) was stirred vigorously and heated under reflux for 1 hr. The mixture was cooled, and unchanged semicarbazone was filtered off and again treated with acid in the above manner. The petroleum solutions were combined, washed with water, dried ($Na_2SO_4$), and evaporated. Chromatography of the residual red oil (5 g.) on alumina (30 g.; Grade IV) from light petroleum (b. p. 40—60°), and elution of the

[15] Girard and Sandulesco, *Helv. Chim. Acta*, 1936, **19**, 1095.

least strongly adsorbed band, gave the ketone (4·5 g.) as a highly unstable, viscous yellow gum. Light absorption: see Table 3.

*Methyl* 2 : 6-*Dimethyl*-8-(2 : 3 : 6-*trimethylphenyl*)*octa*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylate* (X; R = Me).—A mixture of the preceding ketone (4·5 g.), zinc wool (2 g.), methyl bromoacetate (4·5 g.), and benzene (50 c.c.) was heated under reflux until the reaction ceased (½ hr.). Decomposition of the complex, and dehydration of the hydroxy-ester with toluene-*p*-sulphonic acid as in the previous Reformatsky reaction, gave a yellow oil (3·2 g., $n_D^{19}$ 1·64). Chromatography on alumina (200 g.; Grade IV) from light petroleum (b. p. 40—60°), and elution of the least strongly adsorbed band, gave an oil (3·0 g.), $n_D^{18}$ 1·66, $\lambda_{max.}$ 351 mμ ($E_{1\,cm.}^{1\%}$ 700).

The crude ester (2·8 g.) was hydrolysed with boiling methanolic 10% (w/v) potassium hydroxide for 2 hr. The resulting solution was cooled, diluted with water, and then acidified with dilute (1 : 1) phosphoric acid. The liberated acid was extracted with ether. The ethereal solution was washed with water, dried ($Na_2SO_4$), and evaporated to a small volume. The solid (0·4 g.) which had separated was removed and had m. p. (K) 159—163°. Crystallisation of a portion from methanol gave one isomer of 2 : 6-*dimethyl*-8-(2 : 3 : 6-*trimethylphenyl*)*octa*-1 : 3 : 5 : 7-*tetraene*-1-*carboxylic acid* as yellow needles, m. p. (K) 162—163° (Found: C, 80·75; H, 8·4. $C_{20}H_{24}O_2$ requires C, 81·05; H, 8·15%), $\lambda_{max.}$ 349 mμ (ε 44,000). Evaporation of the ethereal mother-liquors gave a yellow solid (0·74 g.), m. p. (K) 140—150°.

A cooled (0°) suspension of the acid (316 mg.; m. p. 159—163°) in ether was treated with excess of ethereal diazomethane. The solvent was evaporated. Chromatography of the residual oil (330 mg.) in light petroleum (b. p. 40—60°) on alumina (30 g.; Grade IV), elution of the yellow band, and evaporation gave a solid (274 mg.). Crystallisation from methanol gave the *ester* (154 mg.) as yellow needles, m. p. (K) 73—75° (Found: C, 81·45; H, 8·7. $C_{21}H_{24}O_2$ requires C, 81·25; H, 8·45%). Light absorption: see Table 3.

The authors thank Messrs. Hoffmann–La Roche (Basle) for the biological assay. One of them (F. G. T.) thanks the University College of Ghana for study leave and another (G. L.) the Halifax Borough Council for a Major Scholarship.

Analyses and light absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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## 378. 1 : 12-2 : 3-10 : 11-*Tribenzoperylene.*

By E. Clar and M. Zander.

An improved synthesis of 2 : 3-10 : 11-dibenzoperylene (II) is described. This reacted easily with maleic anhydride to give the adduct (III) which was dehydrogenated to the anhydride (IV). Decarboxylation yielded the tribenzoperylene (V). The unusually low reactivity of this hydrocarbon is related to formula (Va), which consists exclusively of benzenoid rings interlinked by quasi-single bonds.

2 : 3-10 : 11-Dibenzoperylene (II) was obtained from 9 : 9'-diphenanthryl (I) in a sodium chloride–aluminium chloride melt.[1] However the method gives very low yields and sometimes fails completely.[2] We obtained yields of not less than 50% when the cyclisation was carried out in boiling benzene with aluminium chloride and stannic chloride as dehydrogenating agent.

Recently we assumed the existence of a dissociable adduct between perylene and maleic anhydride preceding the formation of 1 : 12-benzoperylenedicarboxylic anhydride.[3] The two " external " benzene rings in dibenzoperylene (II) stabilise the analogous adduct

[1] Joffe, *Zhur. obshchei Khim.*, 1933, **3**, 524; Zinke and Ziegler, *Ber.*, 1941, **74**, 115; Schauenstein and Bürgermeister, *Ber.*, 1943, **76**, 205; Zinke, *Monatsh.*, 1949, **80**, 202.
[2] Badger, Christie, Pryke, and Sasse, *J.*, 1957, 4417.
[3] Clar and Zander, *J.*, 1957, 4616.

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(III), so that it could be easily isolated in very good yield though it dissociates smoothly into its components in high-boiling solvents. Its absorption spectrum (Fig. 1) which is related to that of 1 : 9-2 : 3-dibenzanthrene [4] supports the assumption of addition in the 1 : 12-positions of the dibenzoperylene (II), as does the fact that dibenzoperylene (II) is readily oxidised in the same positions.[1] Dehydrogenation of the adduct (III) with chloranil gave the anhydride (IV) which was also obtained directly (and quantitatively) from the dibenzoperylene (II) in boiling maleic anhydride containing chloranil. Hydrolysis

FIG. 1.

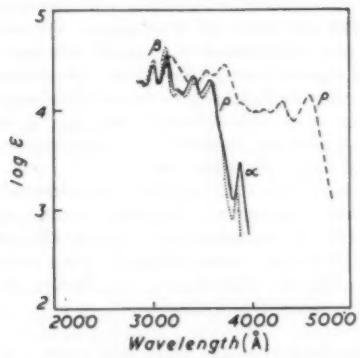



FIG. 2.

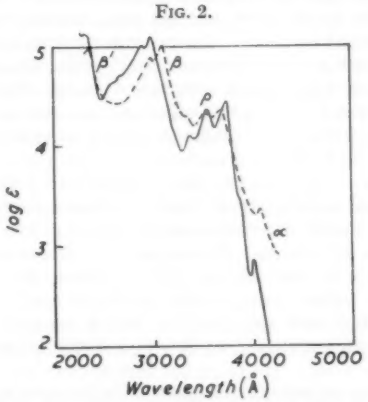



FIG. 1. *Absorption max.* (Å) *and* log ε (*in parentheses*) *of*: (——) *the tetrahydro-anhydride* (III) *in acetic anhydride*: α, 3885 (3·47); *p*, 3590 (4·30), 3410 (4·34), 3245 (4·21); β, 3145 (4·54), 3010 (4046).
(– – –) *The dihydro-anhydride* (VII) *after being boiled in* $C_6H_3Cl_3$ *for* 30 *min. Absorption bands originating from* (VII): *p*, 4580 (4·15), 4310 (4·08), 4140 (4·02). *Absorption bands originating from* (VI): *p*, 3740 (4·46), 3580 (4·41); β, 3200 (4·54).
(. . .) *Maleic anhydride adduct of* (VII) *in acetic anhydride*: α, 3860 (3·16); *p*, 3610 (4·29), 3430 (4·33), 3275 (4·18); β, 3140 (4·64), 3000 (4·49).

FIG. 2. *Absorption max.* (Å) *and* log ε (*in parentheses*) *of*: (——) 1 : 12-2 : 3-10 : 11-*tribenzoperylene* (V) *in* $C_6H_3Cl_3$: α, 4010 (2·86); *p*, 3740 (4·45), 3540 (4·37), 3380 (4·11); *in* EtOH β, 3000 (5·09), 2880 (5·00); β', 2340 (5·14).
(– – –) *Dipotassium* 1 : 12-2 : 3-10 : 11-*tribenzoperylene*-1' : 2'-*dicarboxylate* (*cf.* IV) *in* 50% EtOH: α, 4085 (3·36); *p*, 3680 (4·35), 3520 (4·32); β, 3100 (5·00), 2980 (4·87); β', 2380 (4·99).

and decarboxylation of the anhydride (IV) afforded 1 : 12-2 : 3-10 : 11-tribenzoperylene (V). The absorption spectra of this and of the dicarboxylic acid derived from (IV) are shown in Fig. 2.

An alkaline solution of the dicarboxylic acid derived from the adduct (III) was dehydrogenated by atmospheric oxygen to a yellow acid, derived from (VII). The absorption spectrum of this acid (of VII) shows that it contains the aromatic complex of the dibenzoperylene (II) (Fig. 3). When its solution in trichlorobenzene was boiled the spectrum changed to a type closely related to that of the adduct (III), indicating isomerisation to form (VI) (Fig. 1). The high reactivity of the dibenzoperylene is retained in its derivative (VII) which added another molecule of maleic anhydride to form the adduct (VIII), the spectrum of this further adduct belonged again to type (III)–(VI) (Fig. 1), all these substances being derivatives of 1 : 12-dihydro-2 : 3-10 : 11-dibenzoperylene.

Unlike 1 : 12-2 : 3-8 : 9-tribenzoperylene (IX) which condensed quantitatively [3] with maleic anhydride and chloranil to give the anhydride (X), 1 : 12-2 : 3-10 : 11-tribenzoperylene (V) did not react. The difference between the two hydrocarbons is that the tribenzoperylene (V) can be considered to be a condensed quinquephenyl, as indicated in formula (Va), whilst no analogous arrangement in the isomer (IX) is possible. In the

[4] Clar, *Ber.*, 1943, **76**, 611.

latter at least three double bonds remain outside the benzenoid rings, thus making the molecule sufficiently reactive for the above condensation.

According to formula (Va), 1 : 12-2 : 3-10 : 11-tribenzoperylene contains five benzenoid

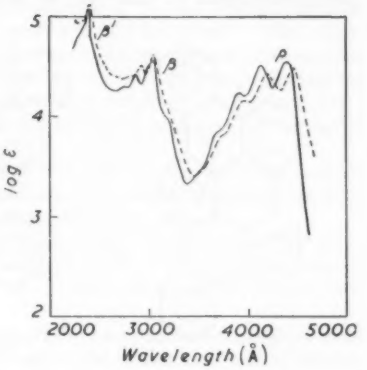
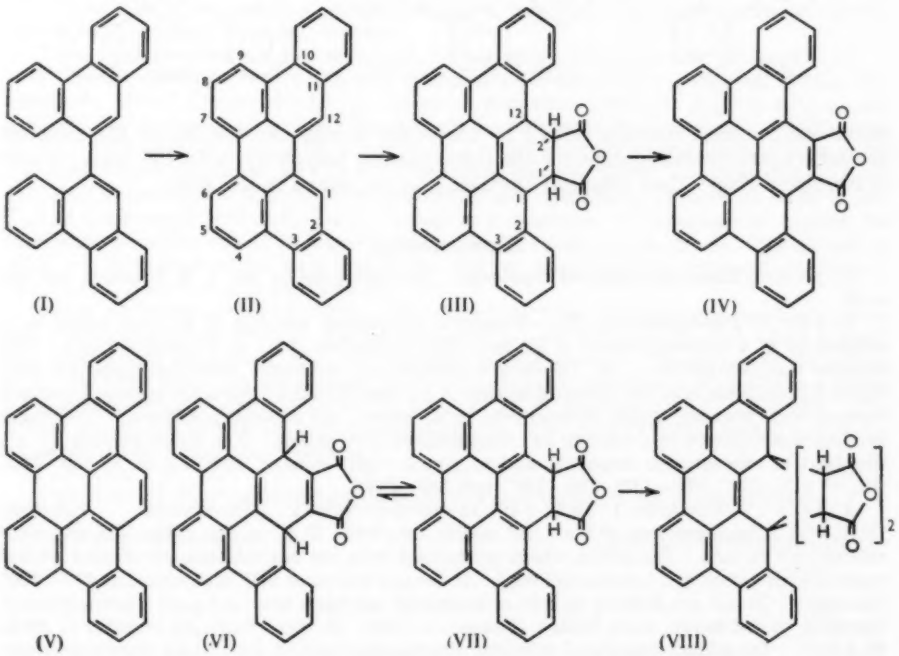



FIG. 3. *Absorption max.* (Å) *and* log ε (*in parentheses*) *of*: (——) 2 : 3-10 : 11-*äibenzoperylene* (II) *in* $C_6H_6$: *p*, 4400 (4·54), 4140 (4·51), 3920 (4·22); *in* EtOH *β*, 3020 (4·54), 2881 (4·41); *β'*, 2380 (5·05). (– – –) *Dipotassium* 1' : 2'-*dihydro*-1 : 12-2 : 3-10 : 11-*tribenzoperylene*-1' : 2'-*dicarboxylate* (*cf.* VII) *in* 50% EtOH: *p*, 4470 (4·48), 4190 (4·42), 3980 (4·16); *β*, 3050 (4·60), 2930 (4·51); *β'*, 2410 (5·10).

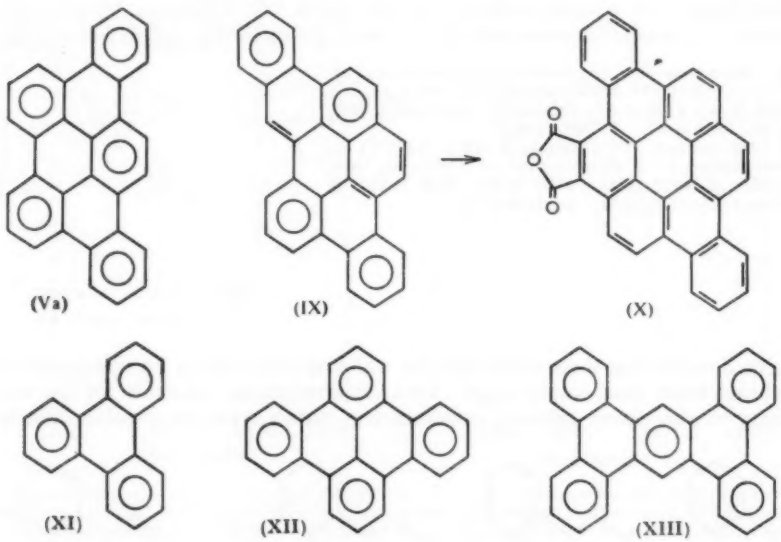
rings (each containing three double bonds) which are interlinked by quasi-single bonds, there being three quasi-empty rings. Such an arrangement accounts for the very low reactivity of the almost colourless hydrocarbon, which does not dissolve even in cold




concentrated sulphuric acid. Formula (Va) represents, not all possible arrangements of the double bonds, but the majority of all Kekulé structures, *i.e.*, the rings indicated by circles are benzenoid.

Only three other hydrocarbons of the tribenzoperylene type (Va) are known, namely,

triphenylene (XI), 1 : 2-6 : 7-dibenzopyrene [5] (XII), and 1 : 2-3 : 4-5 : 6-7 : 8-tetrabenzoanthracene [6] (XIII). These hydrocarbons also do not dissolve in concentrated sulphuric acid to form coloured solutions of the protonated molecules. They show very strong phosphorescence of long life in solid solution at low temperature.[7] Their absorption




bands are the most strongly shifted to the violet among the spectra of the isomeric aromatic hydrocarbons, except for the corresponding polyphenyl with the same number of benzenoid rings; their chemical inertness may be related to this fact.

## Experimental

M. p.s were taken in evacuated capillaries. Microanalyses by Mr. J. M. Cameron and his staff.

2 : 3-10 : 11-*Dibenzoperylene* (II).—Powdered aluminium chloride (1 g.) was added to a solution of 9 : 9′-diphenanthryl [8] (1 g.) and stannic chloride (1 g.) in benzene (10 ml.). The mixture was refluxed for 1 hr. Hydrogen chloride was evolved. After decomposition with dilute hydrochloric acid the dibenzoperylene (1 g.) was filtered off from the organic layer and washed with benzene, dilute hydrochloric acid, water, and aqueous ammonia. The crude product was sublimed in a vacuum and recrystallised from xylene. The yellow needles (0·5 g.) dissolved in concentrated sulphuric acid to give a violet solution and had m. p. 330—332° (lit.,[1,2] 315—318°, 329—332°, 334—336°, and 343—345°).

1 : 12 : 1′ : 2′-*Tetrahydro*-1 : 12-2 : 3-10 : 11-*tribenzoperylene*-1′ : 2′-*dicarboxylic Anhydride* (III).—(*a*) Dibenzoperylene (0·1 g.) and maleic anhydride (3 g.) in dry xylene (30 ml.) were refluxed for 20 min. The *adduct*, which crystallised from the hot solution, was filtered off and washed with xylene and benzene (52 mg.). It became yellow at 250° and melted at 316—320° (decomp.). It did not dissolve in cold concentrated sulphuric acid and gave a green solution changing to red-brown when heated (Found: C, 86·0; H, 4·0. $C_{32}H_{18}O_3$ requires C, 85·3; H, 4·0%). The adduct dissociated in boiling nitrobenzene solution from which dibenzoperylene,

[5] Sako, *Bull. Chem. Soc. Japan*, 1934, **9**, 55; Clar, *Ber.*, 1943, **76**, 609; Lüttringhaus and Schubert, *Naturwiss.*, 1955, **42**, 17; Wittig and Lehmann, *Chem. Ber.*, 1957, **90**, 875.
[6] Lambert and Martin, *Bull. Soc. chim. belges*, 1952, **61**, 124.
[7] Clar and Zander, *Chem. Ber.*, 1956, **89**, 749.
[8] Bachmann, *J. Amer. Chem. Soc.*, 1934, **56**, 1363.

m. p. 332—335°, crystallised on cooling. This hydrocarbon contained a trace of the anhydride (IV), as found in the absorption spectrum.

(*b*) Dibenzoperylene (0·2 g.) and maleic anhydride (5 g.) were refluxed for 30 min. Hot xylene was added to the solution and the precipitated adduct (0·15 g.) filtered off and washed.

1 : 12-2 : 3-10 : 11-*Tribenzoperylene*-1′ : 2′-*dicarboxylic Anhydride* (IV).—(*a*) Dibenzoperylene (1·5 g.) and chloranil (2·5 g.) in maleic anhydride (40 g.) were refluxed for 30 min. Hot nitrobenzene was added and the precipitated orange-red needles were filtered off and washed with nitrobenzene, benzene, and ether (yield 1·95 g.). Sublimation at 380°/0·05 mm., followed by recrystallisation from nitrobenzene, yielded orange-red needles of *anhydride*, m. p. 430—435°, which did not dissolve in cold concentrated sulphuric acid but in the hot acid gave a pale yellow solution (Found: C, 86·1; H, 3·0. $C_{32}H_{14}O_3$ requires C, 86·1; H, 3·2%).

The residue from the sublimation yielded at 500—550°/0·05 mm. a very small amount of a dark violet sublimate which dissolved in dilute alcoholic-aqueous potassium hydroxide to a solution showing absorption bands at 4450, 4100, 3880, 3680, 3340, and 3200 Å.

(*b*) To a boiling solution of chloranil (100 mg.) in trichlorobenzene (5 ml.) the adduct (III) (50 mg.) was added and the whole refluxed for 20 min. The anhydride (IV), which crystallised, was filtered off and extracted with hot xylene (yield 38 mg.). This anhydride did not contain the above by-product.

1 : 12-2 : 3-10 : 11-*Tribenzoperylene* (V).—The anhydride (IV) (1 g.) and soda-lime (3 g.) were ground together and heated to 350° under nitrogen for 45 min. Sublimation at 400°/0·05 mm. gave the *hydrocarbon* (0·5 g.) as pale yellow needles. Recrystallised from xylene they formed plates on slow cooling and needles on quick cooling, both having m. p. 388—389° (Found: C, 95·9; H, 4·15. $C_{36}H_{16}$ requires C, 95·7; H, 4·3%). This tribenzoperylene did not dissolve in cold concentrated sulphuric acid but in the hot acid gave a violet solution. When an alcoholic solution of the hydrocarbon, cooled in liquid oxygen, was irradiated with a quartz lamp it showed a strong greenish-yellow phosphorescence of long life. The cooled crystalline hydrocarbon had an orange-red phosphorescence.

The tribenzoperylene did not react with boiling maleic anhydride and chloranil.

1′ : 2′-*Dihydro*-1 : 12-2 : 3-10 : 11-*tribenzoperylene*-1′ : 2′-*dicarboxylic Anhydride* (VII).—The anhydride (III) (1 g.) was added to a solution of potassium hydroxide (5 g.) in 90% alcohol (100 ml.). A current of air was bubbled through the solution at 60° for 30 min. Acidification of the filtered solution gave a yellow acid (0·8 g.) which on quick recrystallisation from acetic anhydride yielded the *anhydride* (VII) in yellow prisms, decomp. >300°. Concentrated sulphuric acid gave a greenish-blue solution which changed to brown on heating (Found: C, 86·6; H, 4·0. $C_{32}H_{16}O_3$ requires C, 85·7; H, 3·6%. Owing to a tendency to decompose on heating the percentage of carbon tended to higher values when the substance was dried). The anhydride (VII) was isomerised to the form (VI) at 80—100° or when boiled in trichlorobenzene for a short time. This change is shown in Fig. 1.

*Maleic Anhydride Diadduct* (VIII).—The anhydride (VII) (50 mg.) and maleic anhydride (2 g.) were refluxed for 10 min. The adduct began to crystallise from the hot solution which was diluted with hot xylene; the solid was collected and washed. The prisms of the *adduct*, m. p. 364° (decomp.), did not dissolve in cold concentrated sulphuric acid and gave a yellow solution on heating (Found: C, 78·8; H, 3·35. $C_{36}H_{18}O_6$ requires C, 79·1; H, 3·3%). The adduct dissociated in boiling trichlorobenzene into the compound (VII) and maleic anhydride, as shown by the absorption spectrum.

One of us (M. Z.) thanks Rütgerswerke A.G., Frankfurt/Main, for a scholarship.

UNIVERSITY OF GLASGOW. [*Received, December 23rd*, 1957.]

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## 379. *An Addition Compound of Tetraethylammonium Bromide and Succinimide.*

By H. M. Powell and E. Wait.

A compound previously formulated in a different way has been shown to be a lattice compound containing tetraethylammonium and bromide ions and succinimide molecules. The principle of the structure is local neutralisation of charges with the positive NH group of succinimide directed towards the negative ions, the negative oxygen atoms of the succinimide towards the positive ions, and negative and positive ions themselves in close contact.

There are many crystalline substances containing molecules of more than one kind, which together build up the crystal structure as a whole without ordinary chemical linkages between the components of different sorts.[1] Intermolecular attractions between the different components are of the van der Waals type. Some related structures exist in which one of the combining substances is molecular and the other ionic. For instance, $Cs_3As_2Cl_9$ has a structure which contains $AsCl_3$ molecules with cæsium and chloride ions;[2] the compounds sucrose–sodium bromide[3] and cysteinylglycine–sodium iodide[4] are also of this type.

Braude and Waight[5] called attention to the compound under investigation, for which they had suggested a formula. It seemed likely that it might be another example of a lattice compound with $(Et_4N)Br$ as the ionic and succinimide as the molecular constituent. The preparation of this compound and of its chloride analogue by crystallisation of chloroform solutions of the appropriate components in equimolar proportions lent support to this hypothesis. Accordingly an *X*-ray crystallographic examination was undertaken.

The bromide crystals prepared as above were unsuitable for detailed *X*-ray analysis and those used were from a sample provided by Professor Braude. This was extracted from the solid residues of the reaction of *cyclo*hexene with *N*-bromosuccinimide carried out with tetraethylammonium bromide as a catalyst.[5] The chloride was deliquescent, but the bromide remained unchanged under normal atmospheric conditions. The composition of the *chloride* was established by analysis (Found: C, 53·2; H, 8·27; N, 11·1; Cl, 9·75. $C_{16}H_{30}O_4N_2Cl$ requires C, 52·9; H, 8·26; N, 11·6; Cl, 9·77%). The densities were measured by flotation and were, for the bromide 1·370 ± 0·005 g./c.c., and for the chloride 1·235 ± 0·005 g./c.c.

For the *X*-ray investigation Cu-$K_\alpha$ radiation was used. Oscillation and equi-inclination Weissenberg techniques were used to measure intensities of *X*-ray reflections. Unit-cell dimensions were deduced from high-angle axial reflections on Weissenberg photographs calibrated with copper-powder lines. Two crystals elongated respectively along *a* and *b* were used for the 0*kl* and *h*0*l* zones of the bromide. The chloride crystals were needles elongated along *b*. An equidimensional fragment cut from such a needle and coated with a mixture of Vaseline and liquid paraffin was used for the 0*kl* zone. Crystals could thus be preserved for about 24 hr. Relative intensities of reflections, recorded by the multiple-film technique, were measured by visual comparison with a scale of standard spots prepared with a crystal.

The bromide and chloride form similar structures. Oscillation photographs about two mutually perpendicular axes have equatorial symmetry and, with the cell dimensions and optically biaxial behaviour, establish orthorhombic symmetry. The bromide has $a = 7{\cdot}52 \pm 0{\cdot}02$, $b = 18{\cdot}76 \pm 0{\cdot}05$, $c = 27{\cdot}90 \pm 0{\cdot}10$ Å, and the chloride $a = 7{\cdot}56 \pm 0{\cdot}02$, $b = 18{\cdot}78 \pm 0{\cdot}05$, $c = 27{\cdot}70 \pm 0{\cdot}10$ Å. For eight formula units $C_{16}H_{30}O_4N_2X$

[1] Powell, *J.*, 1954, 2658.
[2] Hoard and Goldstein, *J. Chem. Phys.*, 1935, **3**, 199.
[3] Beevers and Cochran, *Proc. Roy. Soc.*, 1947, *A*, **190**, 257.
[4] Dyer, *Acta Cryst.*, 1951, **4**, 42.
[5] Braude and Waight, *J.*, 1952, 1116.

per cell, the calculated densities are 1·379 g./c.c. for X = Br and 1·238 g./c.c. for X = Cl, in good agreement with the measured values.

The absent spectra, $0kl$, $k \neq 2n$, $h0l$, $l \neq 2n$, and $hk0$, $h \neq 2n$, show that the space-group of both compounds is *Pbca*.

The general position in the space-group is of 8-fold multiplicity and there are special 4-fold positions coinciding with symmetry centres. Patterson projections perpendicular to [100] and [010] gave the positions of the bromide atoms, showing that they do not occupy the special positions. All atoms were therefore assumed to be in general positions.

FIG. 1.

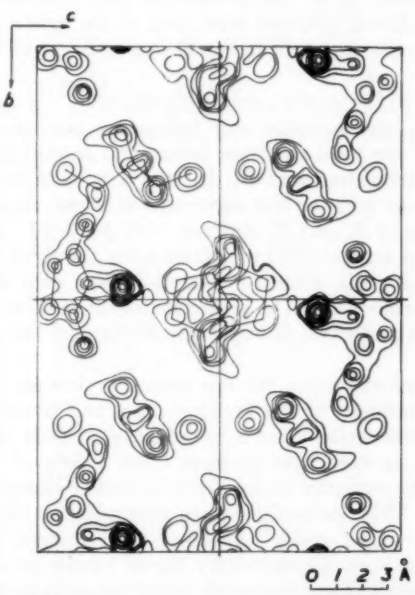


FIG. 2.

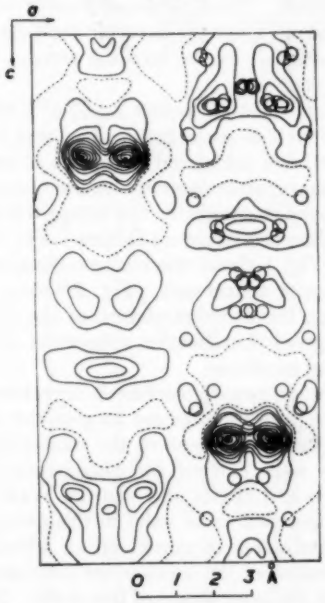


FIG. 1. *Electron density projected perpendicular to* [100]. *The origin of the unit cell is at the centre of the figure which shows the area from* $-b/2$ *to* $b/2$ *and* $-c/4$ *to* $c/4$. *Contours are at arbitrary equal intervals, approximately 2 electrons/Å*$^2$ *and at five times that interval on bromine atoms which are represented by the four high peaks. Some of the succinimide molecules and a tetraethylammonium ion are indicated in outline.*

FIG. 2. *Electron density projected perpendicular to* [010]. *The origin of the unit cell is at the centre of the figure which shows the area from* $-c/4$ *to* $c/4$ *and* $-a/2$ *to* $a/2$. *The high peaks correspond to bromine. In the right half the lighter atoms are indicated by circles.*

Approximate co-ordinates for the bromine are $x = 0{\cdot}176$, $z = 0{\cdot}135$. For $y$ the value is 0·026 or $\frac{1}{4} - 0{\cdot}026$. The ambiguity, which is unresolvable in the two projections used, does not interfere with the refinement of the [100] projection by Fourier F synthesis. The change of the co-ordinate of the bromine atom from $y$ to $\frac{1}{4} - y$ leaves the sign of its contribution to $F_{0kl}$ unchanged if $k = 4n$ but reversed if $k = 4n + 2$. Fourier syntheses based on the two sets of signs appear the same if the $y$ axis is reversed in direction and the origin is transferred to $y = \frac{1}{4}$. Similarly, when differences between $F_{0kl}$ from bromide and chloride are considered the ambiguity has the same effect.

A Fourier synthesis based on $F_{0kl}$ with the signs determined by bromine contributions alone did not lead directly to further development of the structure. On the assumption that the halogen parameters were sufficiently close for application of the isomorphous

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replacement method, a set of signs was obtained by comparison of the intensities of corresponding reflections of the bromide and chloride crystals. The absolute scale of the observed structure factors and an approximate average value for the temperature factor were determined for each compound by Wilson's method.[6] The resulting Fourier syntheses for the two compounds were very similar. Several features common to both could be interpreted as atomic groups that might be expected in the structure. These included the tetraethylammonium group and one succinimide molecule. The projection perpendicular to [010] with signs based on the heavy-atom contribution was calculated for the bromide. This showed the same succinimide molecule edge-on and indicated its slope. The position of the remaining succinimide molecule was also suggested by this projection. Three cycles of Fourier refinement of the [100] projection now followed. At the second stage an isotropic temperature factor, different from that of the light atoms, was assigned to the bromine atom. Thus the structure factor F was assumed to be of the form:

$$n\{F_{Br} \exp [-(B_1/\lambda^2) \sin^2 \theta] + F_{O,N,O} \exp [-(B_2/\lambda^2) \sin^2 \theta]\}$$

where $n$ is a scale factor, $F_{Br}$ and $F_{O,N,O}$ the bromine and light-atom contributions respectively calculated for atoms at rest, F the total structure factor, and $B_1$ and $B_2$ the two temperature factors. A least-squares procedure with $B_1$, $B_2$, and $n$ as variables was employed to determine the values which would give the best agreement between calculated and observed structure factors. The values of $B_1$ and $B_2$ obtained were $B_1 = 2{\cdot}1$, $B_2 = 5{\cdot}0$. Fig. 1 shows the electron-density map for the [100] projection after the third stage of Fourier refinement. Fig. 2 shows a much less accurate electron-density map, based only on the bromine phases, of the [010] projection. The projection distance of 18·76 Å is so great that Fourier refinement on this projection is impossible because of the overlapping of atoms.

The proposed structure is therefore based mainly on the one refined projection. The second projection served to give the $x$ co-ordinate of the bromine atom and to indicate the relative positions of the molecular components. The $x$ co-ordinates of most of the atoms were derived by consideration of the molecular packing. The values of bond lengths and angles and van der Waals radii normally encountered in similar compounds were assumed to be valid in this case also. The various distances were adjusted and the $x$ co-ordinates measured on an adjustable "wire spoke" model of the structure. The dimensions of the succinimide molecule have been determined by Mason [7] and were available in the later stages of this work. Independent measurements of the tetraethylammonium ion were obtained by the study of tetraethylammonium iodide (see following paper). The conformation [Fig. 1(*A*), following paper] of the ion is different in the two compounds but it is likely that the distortions of the $N{-}C_{(1)}{-}C_{(2)}$ bond angle observed in the iodide also occur in the molecular compound. A significantly better fit with the [100] projection was obtained by the use of a distorted model for the tetraethylammonium ion.

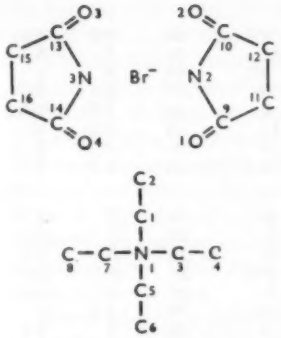
When the three-dimensional model had been constructed, some twenty intermolecular approach distances which had not been used as criteria for determining $x$ co-ordinates were examined and were found all to be consistent with accepted values of van der Waals radii. This constitutes the main evidence for the correctness of the three-dimensional structure suggested.

Table 1 lists the estimated co-ordinates of the atoms as fractions of the unit cell edge. The $y$ and $z$ co-ordinates are derived from the refined [100] projection and are more accurate than the $x$ co-ordinates which, with the exception of those of the bromide ion and $N_{(2)}$ are derived from packing studies.

Derived inter-atomic distances are not listed since many of these were assumed for the determination of the $x$ co-ordinates. Table 2 lists calculated and observed structure factors for the [100] projection. The discrepancy factor $R = \sum||F_o| - |F_c||/\sum|F_o| = 0{\cdot}26$

[6] Wilson, *Nature*, 1942, **150**, 152.
[7] Mason, *Acta Cryst.*, 1956, **9**, 405.

TABLE 1. *Atomic co-ordinates.*



| | *x* | *y* | *z* | | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|
| Br | 0·175 | 0·025 | 0·134 | $C_{(11)}$ | $\bar{0}\cdot\bar{1}\bar{0}\bar{0}$ | 0·068 | 0·227 |
| $C_{(1)}$ | 0·067 | 0·2783 | 0·105 | $C_{(12)}$ | $\bar{0}\cdot\bar{4}\bar{0}\bar{0}$ | 0·487 | 0·230 |
| $C_{(2)}$ | $\bar{0}\cdot\bar{0}\bar{5}\bar{3}$ | 0·207 | 0·093 | $N_{(2)}$ | $\bar{0}\cdot\bar{3}\bar{6}\bar{7}$ | 0·033 | 0·182 |
| $C_{(3)}$ | 0·375 | 0·222 | 0·087 | $O_{(1)}$ | $\bar{0}\cdot\bar{3}\bar{3}\bar{3}$ | 0·147 | 0·183 |
| $C_{(4)}$ | 0·472 | 0·247 | 0·038 | $O_{(2)}$ | $\bar{0}\cdot\bar{1}\bar{6}\bar{7}$ | 0·412 | 0·187 |
| $C_{(5)}$ | 0·200 | 0·212 | 0·170 | $C_{(13)}$ | $\bar{0}\cdot\bar{2}\bar{6}\bar{7}$ | 0·050 | 0·015 |
| $C_{(6)}$ | 0·100 | 0·250 | 0·208 | $C_{(14)}$ | $\bar{0}\cdot\bar{2}\bar{0}\bar{0}$ | 0·438 | 0·022 |
| $C_{(7)}$ | 0·365 | 0·330 | 0·135 | $C_{(15)}$ | $\bar{0}\cdot\bar{3}\bar{5}\bar{0}$ | 0·045 | 0·058 |
| $C_{(8)}$ | $\bar{0}\cdot\bar{4}\bar{5}\bar{0}$ | 0·318 | 0·155 | $C_{(16)}$ | $\bar{0}\cdot\bar{1}\bar{3}\bar{3}$ | 0·460 | 0·067 |
| $N_{(1)}$ | 0·250 | 0·263 | 0·123 | $N_{(3)}$ | 0·242 | 0·008 | 0·012 |
| $C_{(9)}$ | $\bar{0}\cdot\bar{2}\bar{6}\bar{7}$ | 0·088 | 0·200 | $O_{(3)}$ | 0·300 | 0·413 | 0·012 |
| $C_{(10)}$ | $\bar{0}\cdot\bar{2}\bar{3}\bar{3}$ | 0·473 | 0·202 | $O_{(4)}$ | $\bar{0}\cdot\bar{2}\bar{6}\bar{7}$ | 0·388 | 0·013 |

TABLE 2. *Observed structure amplitudes and calculated structure factors for hkl.* (In each set of three columns the first lists values of *l*, the second $F_{calc.}/10$, and the third $F_{obs.}/10$.)

*00l*

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 3·5 | 4·5 | 12 | $\bar{6}\cdot\bar{5}$ | 8·5 | 22 | 12 | 13·5 | 32 | $\bar{5}$ | 2 |
| 4 | $\bar{1}\bar{0}\cdot\bar{5}$ | 15·5 | 14 | 14 | 12 | 24 | $\bar{0}\cdot\bar{5}$ | 3·5 | 34 | 5 | 5 |
| 6 | 29·5 | 28 | 16 | 19·5 | 16 | 26 | $\bar{7}\cdot\bar{5}$ | 10 | | | |
| 8 | 16 | 13 | 18 | $\bar{9}$ | 11·5 | 28 | $\bar{1}\cdot\bar{5}$ | 3·5 | | | |
| 10 | 11 | 9·5 | 20 | $\bar{5}\cdot\bar{5}$ | 8 | 30 | 6·5 | 7 | | | |

*02l*

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 36·5 | 29·5 | 9 | $\bar{3}$ | 6·5 | 18 | $\bar{9}$ | 9 | 27 | $\bar{1}$ | 1·5 |
| 1 | $\bar{9}\cdot\bar{5}$ | 9 | 10 | $\bar{4}\cdot\bar{5}$ | 8·5 | 19 | 1 | 2·5 | 28 | $\bar{1}$ | 1·5 |
| 2 | $\bar{2}\cdot\bar{5}$ | 1 | 11 | 1·5 | 6 | 20 | $\bar{5}$ | 6 | 29 | 1·5 | 1·5 |
| 3 | 0 | 3 | 12 | $\bar{8}$ | 7 | 21 | 5 | 6 | 30 | 6·5 | 6 |
| 4 | 15·5 | 11 | 13 | 2 | 5·5 | 22 | 9·5 | 9 | 31 | $\bar{1}\cdot\bar{5}$ | 1·5 |
| 5 | 1·5 | 3·5 | 14 | 17·5 | 17 | 23 | $\bar{1}\cdot\bar{5}$ | 3 | 32 | $\bar{1}\cdot\bar{5}$ | 3 |
| 6 | 20·5 | 18·5 | 15 | 1 | 6 | 24 | $\bar{2}$ | 6 | 33 | 0·5 | 0 |
| 7 | $\bar{0}\cdot\bar{5}$ | 4·5 | 16 | 18 | 17·5 | 25 | $\bar{2}$ | 1·5 | 34 | $\bar{5}$ | 5 |
| 8 | 19·5 | 14·5 | 17 | $\bar{4}\cdot\bar{5}$ | 6 | 26 | $\bar{9}\cdot\bar{5}$ | 6 | 35 | 1·5 | 0 |

*04l*

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 49·5 | 44 | 9 | $\bar{2}\bar{2}$ | 17·5 | 18 | $\bar{8}$ | 6 | 27 | 3 | 3·5 |
| 1 | $\bar{1}\bar{3}$ | 15 | 10 | $\bar{8}$ | 9·5 | 19 | 1 | 3 | 28 | 1 | 2·5 |
| 2 | 6·5 | 1 | 11 | $\bar{5}$ | 0 | 20 | $\bar{5}$ | 5 | 29 | 3 | 3 |
| 3 | $\bar{1}\bar{0}$ | 5·5 | 12 | $\bar{1}\bar{2}\cdot\bar{5}$ | 13·5 | 21 | 4 | 6·5 | 30 | 6 | 5·5 |
| 4 | $\bar{1}\bar{8}$ | 21 | 13 | 13·5 | 21 | 22 | 5 | 7·5 | 31 | $\bar{3}\cdot\bar{5}$ | 4·5 |
| 5 | 14·5 | 21 | 14 | 10 | 8 | 23 | $\bar{5}$ | 3·5 | 32 | $\bar{1}\bar{0}$ | 2·5 |
| 6 | $\bar{5}\cdot\bar{5}$ | 10·5 | 15 | $\bar{2}\cdot\bar{5}$ | 0 | 24 | 2·5 | 3 | 33 | $\bar{2}$ | 2·5 |
| 7 | 9 | 12 | 16 | 4·6 | 3·5 | 25 | $\bar{3}\cdot\bar{5}$ | 3·5 | 34 | $\bar{3}\cdot\bar{5}$ | 2·5 |
| 8 | 14·5 | 10·5 | 17 | 8 | 5 | 26 | $\bar{6}\cdot\bar{5}$ | 8 | 35 | 2·5 | 0 |

*06l*

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 1·5 | 0 | 9 | $\bar{1}\bar{4}$ | 17 | 18 | $\bar{6}\cdot\bar{5}$ | 5 | 27 | 2·5 | 3 |
| 1 | $\bar{1}\bar{2}\cdot\bar{5}$ | 14·5 | 10 | $\bar{8}\cdot\bar{5}$ | 12·5 | 19 | $\bar{1}\cdot\bar{5}$ | 0 | 28 | 0·5 | 0 |
| 2 | $\bar{5}\cdot\bar{5}$ | 6·5 | 11 | $\bar{1}\cdot\bar{5}$ | 1·5 | 20 | $\bar{4}$ | 3·5 | 29 | 2·5 | 2 |
| 3 | $\bar{1}\bar{3}\cdot\bar{5}$ | 18 | 12 | $\bar{6}$ | 3·5 | 21 | 8 | 9 | 30 | 3·5 | 3·5 |
| 4 | $\bar{1}\bar{8}\cdot\bar{5}$ | 18 | 13 | 5 | 4·5 | 22 | 5·5 | 5·5 | 31 | $\bar{4}\cdot\bar{5}$ | 4 |
| 5 | $\bar{8}$ | 13 | 14 | 8·5 | 8 | 23 | $\bar{5}$ | 5·5 | 32 | $\bar{0}\cdot\bar{5}$ | 0 |
| 6 | 0 | 4·5 | 15 | $\bar{6}\cdot\bar{5}$ | 4·5 | 24 | 0 | 0 | 33 | $\bar{2}$ | 0 |
| 7 | $\bar{5}$ | 0 | 16 | 4·5 | 4·5 | 25 | $\bar{7}\cdot\bar{5}$ | 9 | 34 | 2·5 | 2·5 |
| 8 | 8 | 9 | 17 | $\bar{1}\bar{4}\cdot\bar{5}$ | 8·5 | 26 | $\bar{6}$ | 4·5 | | | |

*08l*

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 2·5 | 7·5 | 9 | $\bar{1}\bar{6}$ | 17·5 | 18 | $\bar{2}\cdot\bar{5}$ | 1·5 | 27 | $\bar{4}\cdot\bar{5}$ | 6 |
| 1 | $\bar{1}\bar{5}\cdot\bar{5}$ | 11 | 10 | $\bar{2}\cdot\bar{5}$ | 0 | 19 | $\bar{0}\cdot\bar{5}$ | 1·5 | 28 | 1 | 0 |
| 2 | $\bar{5}\cdot\bar{5}$ | 1 | 11 | $\bar{1}\bar{2}$ | 8·5 | 20 | $\bar{1}$ | 0 | 29 | 2 | 1·5 |
| 3 | $\bar{1}\bar{1}\cdot\bar{5}$ | 10·5 | 12 | $\bar{3}\cdot\bar{5}$ | 5·5 | 21 | 6·5 | 7 | 30 | 2 | 0 |
| 4 | $\bar{6}\cdot\bar{5}$ | 1·5 | 13 | 6·5 | 8·5 | 22 | 1·5 | 1·5 | 31 | $\bar{4}$ | 2·5 |
| 5 | 16 | 17·5 | 14 | $\bar{1}$ | 0 | 23 | $\bar{8}\cdot\bar{5}$ | 8 | 32 | 3 | 0 |
| 6 | $\bar{3}\cdot\bar{5}$ | 6·5 | 15 | 1·5 | 2·5 | 24 | 1·5 | 1·5 | 33 | $\bar{3}\cdot\bar{5}$ | 1·5 |
| 7 | $\bar{3}$ | 3·5 | 16 | 3 | 2 | 25 | $\bar{5}\cdot\bar{5}$ | 6·5 | | | |
| 8 | 0 | 6·5 | 17 | 16 | 13·5 | 26 | $\bar{2}$ | 2·5 | | | |

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TABLE 2. (*Continued.*)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 010*l* | | | | | | |
| 0 | $\bar{4}$ | 3·5 | 8 | $\bar{1}$ | 2 | 16 | $\bar{1}\cdot\bar{5}$ | 3·5 | 24 | 0·5 | 2·5 |
| 1 | $\bar{13}\cdot\bar{5}$ | 13 | 9 | $\bar{13}\cdot\bar{5}$ | 13·5 | 17 | $\bar{14}\cdot\bar{5}$ | 11 | 25 | $\bar{7}$ | 8 |
| 2 | $\bar{1}\cdot\bar{5}$ | 1·5 | 10 | 2 | 6 | 18 | $\bar{1}$ | 2·5 | 26 | 0 | 0 |
| 3 | $\bar{14}\cdot\bar{5}$ | 14 | 11 | $\bar{1}\cdot\bar{5}$ | 3·5 | 19 | 1·5 | 0 | 27 | 4·5 | 6 |
| 4 | $\bar{4}\cdot\bar{5}$ | 6·5 | 12 | 3·5 | 5·5 | 20 | 0·5 | 0 | 28 | $\bar{0}\cdot\bar{5}$ | 3·5 |
| 5 | $\bar{17}\cdot\bar{5}$ | 19 | 13 | 8·5 | 6 | 21 | 9·5 | 11 | 29 | 2·5 | 0 |
| 6 | $\bar{3}$ | 0 | 14 | 1·5 | 0 | 22 | 0·5 | 0 | 30 | 0 | 3 |
| 7 | $\bar{2}$ | 2·5 | 15 | $\bar{3}$ | 0 | 23 | $\bar{5}\cdot\bar{5}$ | 4·5 | 31 | 3·5 | 0 |
| | | | | | 012*l* | | | | | | |
| 0 | $\bar{5}$ | 4·5 | 8 | $\bar{4}$ | 2·5 | 16 | $\bar{0}\cdot\bar{5}$ | 3 | 24 | $\bar{1}$ | 0 |
| 1 | $\bar{5}$ | 4·5 | 9 | $\bar{11}\cdot\bar{5}$ | 11·5 | 17 | $\bar{8}\cdot\bar{5}$ | 7 | 25 | $\bar{5}$ | 5·5 |
| 2 | $\bar{4}\cdot\bar{5}$ | 5·5 | 10 | 1·5 | 0 | 18 | 1·5 | 0 | 26 | 3 | 3·5 |
| 3 | $\bar{10}\cdot\bar{5}$ | 9 | 11 | $\bar{5}$ | 3·5 | 19 | 2·5 | 1·5 | 27 | 4·5 | 4·5 |
| 4 | 3·5 | 6 | 12 | $\bar{3}$ | 3·5 | 20 | 2 | 0 | 28 | 0 | 3·5 |
| 5 | 10·5 | 11 | 13 | 9 | 11 | 21 | 6·5 | 4·5 | 29 | 3·5 | 3 |
| 6 | 0·5 | 1·5 | 14 | $\bar{4}$ | 4·5 | 22 | $\bar{2}\cdot\bar{5}$ | 3 | 30 | $\bar{1}$ | 2·5 |
| 7 | 5·5 | 8 | 15 | 0 | 0 | 23 | $\bar{3}\cdot\bar{5}$ | 0 | | | |
| | | | | | 014*l* | | | | | | |
| 0 | $\bar{10}$ | 10·5 | 8 | $\bar{6}$ | 6·5 | 16 | $\bar{3}\cdot\bar{5}$ | 8 | 24 | $\bar{0}\cdot\bar{5}$ | 2 |
| 1 | $\bar{5}$ | 4 | 9 | $\bar{8}\cdot\bar{5}$ | 6·5 | 17 | $\bar{7}$ | 5·5 | 25 | $\bar{3}\cdot\bar{5}$ | 2·5 |
| 2 | 0 | 3 | 10 | 5·5 | $\bar{6}$ | 18 | 4·5 | 4·5 | 26 | 3·5 | 2·5 |
| 3 | $\bar{5}$ | 4 | 11 | $\bar{0}\cdot\bar{5}$ | 0 | 19 | 2·5 | 2·5 | 27 | 3·5 | 3 |
| 4 | 5 | 6·5 | 12 | 7·5 | 8·5 | 20 | 1 | 0 | 28 | $\bar{0}\cdot\bar{5}$ | 0·5 |
| 5 | 10 | 6 | 13 | 8 | 3·5 | 21 | 6 | 3·5 | 29 | 2·5 | 0 |
| 6 | $\bar{4}$ | 6 | 14 | $\bar{5}\cdot\bar{5}$ | 7 | 22 | $\bar{3}$ | 2 | | | |
| 7 | 2 | 2·5 | 15 | $\bar{0}\cdot\bar{5}$ | 0 | 23 | $\bar{2}$ | 2·5 | | | |
| | | | | | 016*l* | | | | | | |
| 0 | $\bar{12}\cdot\bar{5}$ | 11 | 7 | 2·5 | 3 | 14 | $\bar{4}\cdot\bar{5}$ | 1·5 | 21 | 4 | 0 |
| 1 | $\bar{6}$ | 7 | 8 | $\bar{3}\cdot\bar{5}$ | 0 | 15 | 0 | 1·5 | 22 | $\bar{5}$ | 4·5 |
| 2 | $\bar{0}\cdot\bar{5}$ | 4·5 | 9 | $\bar{4}\cdot\bar{5}$ | 5·5 | 16 | $\bar{5}\cdot\bar{5}$ | 5·5 | 23 | 1 | 0 |
| 3 | $\bar{4}\cdot\bar{5}$ | 4·5 | 10 | 1 | 0 | 17 | $\bar{4}$ | 5 | 24 | 0·5 | 0 |
| 4 | 7·5 | 11 | 11 | $\bar{1}\cdot\bar{5}$ | 3·5 | 18 | 5 | 5·5 | 25 | $\bar{2}\cdot\bar{5}$ | 3·5 |
| 5 | 7 | 7 | 12 | 2·5 | 3 | 19 | 2 | 0 | 26 | 4·5 | 4 |
| 6 | $\bar{3}\cdot\bar{5}$ | 3·5 | 13 | 5 | 3 | 20 | 2 | 0 | 27 | 1·5 | 0 |
| | | | | | 018*l* | | | | | | |
| 0 | $\bar{11}$ | 5·5 | 7 | 1·5 | 0 | 14 | $\bar{4}$ | 2·5 | 21 | $\bar{1}\cdot\bar{5}$ | 0 |
| 1 | 0·5 | 0 | 8 | $\bar{5}$ | 0 | 15 | 0 | 0 | 22 | 4 | 3 |
| 2 | 1·5 | 4·5 | 9 | $\bar{2}\cdot\bar{5}$ | 1·5 | 16 | $\bar{5}$ | 5·5 | 23 | $\bar{1}$ | 0 |
| 3 | 0·5 | 0 | 10 | 4 | 3·5 | 17 | 1 | 0 | 24 | 0·5 | 0 |
| 4 | 6 | 7 | 11 | $\bar{0}\cdot\bar{5}$ | 0 | 18 | 5·5 | 5·5 | 25 | $\bar{1}$ | 0 |
| 5 | 2 | 0 | 12 | 6·5 | 6·5 | 19 | 0·5 | 0 | | | |
| 6 | $\bar{3}\cdot\bar{5}$ | 1·5 | 13 | 2·5 | 0 | 20 | 2·5 | 2 | | | |
| | | | | | 020*l* | | | | | | |
| 0 | $\bar{8}$ | 6 | 6 | 1·5 | 0 | 12 | 5 | 3 | 18 | 4·5 | 2·5 |
| 1 | $\bar{1}$ | 0 | 7 | 0·5 | 0 | 13 | 0·5 | 0 | 19 | $\bar{0}\cdot\bar{5}$ | 0 |
| 2 | 1·5 | 3·5 | 8 | $\bar{5}\cdot\bar{5}$ | 3·5 | 14 | $\bar{4}$ | 3 | 20 | 2 | 1 |
| 3 | $\bar{0}\cdot\bar{5}$ | 0 | 9 | 0 | 0 | 15 | $\bar{0}\cdot\bar{5}$ | 0 | | | |
| 4 | 7·5 | 8·5 | 10 | 4 | 3·5 | 16 | $\bar{3}$ | 2 | | | |
| 5 | 1 | 0 | 11 | 0·5 | 0 | 17 | 0·5 | 0 | | | |
| | | | | | 022*l* | | | | | | |
| 0 | $\bar{6}$ | 3·5 | 4 | 4·5 | 3 | 8 | $\bar{4}\cdot\bar{5}$ | 3·5 | 12 | 4 | 2·5 |
| 1 | 2 | 2·5 | 5 | $\bar{1}$ | 1·5 | 9 | 1·5 | 2 | 13 | $\bar{1}\cdot\bar{5}$ | 0 |
| 2 | 0·5 | 0 | 6 | $\bar{1}$ | 0 | 10 | 3 | 1·5 | 14 | $\bar{3}$ | 2 |
| 3 | 2 | 0 | 7 | $\bar{0}\cdot\bar{5}$ | 2 | 11 | 0 | 0 | 15 | 0·5 | 0 |
| | | | | | 024*l* | | | | | | |
| 0 | $\bar{4}$ | 1 | 2 | 0·5 | 0 | 4 | 3·5 | 1 | 6 | $\bar{1}\cdot\bar{5}$ | 0·5 |
| | 12 | 1·5 | 3 | 1·5 | 0 | 5 | $\bar{2}\cdot\bar{5}$ | 1·5 | | | |

which is not unsatisfactory for a structure of this complexity. Fig. 3 gives a general view of the structure down [100].

The groups of atoms identified in the structure and their dispositions relative to each other are such that the molecular formula proposed by Braude and Waight [5] must be rejected. The tetraethylammonium and bromide ions and the succinimide molecule

retain their individuality in the structure. All like ions are structurally equivalent but the succinimide molecules are of two crystallographically different kinds. The structure as a whole may be considered in relation to the cohesion between its three components.

The shortest distances between any of them are those (3·4 Å) between the bromide ions and the nitrogen atoms of succinimide molecules. Compared with 3·3 Å for the bromide ion to OH distance in sucrose–sodium bromide, this suggests a weak hydrogen bond. Otherwise the components are at distances corresponding to ionic or van der Waals radii. The only distinguishable complex of finite size formed by the three components is this group of one bromide ion and two succinimide molecules, one of each crystallographic kind. If this is regarded as a form of complex negative ion the structure as a whole consists of sheets of tetraethylammonium ions parallel to (010) carrying a positive charge and spaced at $b/2$ or about 9·9 Å from each other. The negatively charged complexes form parallel sheets between them.

Alternatively, a description may begin with the electrostatic interaction of bromide and tetraethylammonium ions. The latter have roughly the form of oblate spheroids.

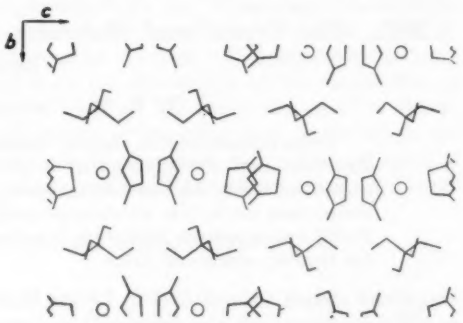


FIG. 3. *The structure as seen along the a axis. The origin is at the centre of the figure.*

(Circles = bromine ions. Branched pentagons, some overlapping in pairs, = succinimide molecules. Insect-like figures show the C–C and C–N bonds of tetraethylammonium ions.)

They are arranged with their short axes roughly parallel to $b$. Each has two bromide ions in the general directions of its minor axes, one on each side at a distance of about 4·7 Å. Sheets of tetraethylammonium are joined by negative bromide ions which lie roughly above and below the positive centres. The bromide ions have diameters considerably smaller than the major axis of the tetraethylammonium spheroid and therefore cannot completely fill the sheet of the same area. In this sense the succinimide molecules may be said to fill the spaces left by the arrangement of the positive and negative ions.

Another description emphasises the interaction of tetraethylammonium and succinimide. The oxygen atoms of the succinimide molecules will carry some negative charge, and both oxygen atoms of both kinds of succinimide molecule are found to be directed towards a positive tetraethylammonium ion. In this way succinimide molecules form bridges linking the different positive sheets. There is a certain coherence of the complex ions and succinimide molecules to form a three-dimensional extended structure which as a whole is positively charged. The negative ions may be described as placed in the holes of this structure. From this point of view the behaviour in the series of halides is explicable. The bromide ion just fits the hole. The smaller chloride ion therefore does not completely fill the space and the deliquescence of the compound containing it may be connected with the consequent instability. The iodide ion is too large for the hole and the corresponding compounds could not be prepared.

The general constructional principle of the whole is therefore that of local neutralisation of charges; the positive NH part of succinimide is directed towards the negative ions, the negative oxygens of the succinimide towards the positive ions, and the negative and positive ions themselves are in close contact.

The structure is related to " co-ordination structures " in V. M. Goldschmidt's sense.

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Complete co-ordination of the various components, with the limitations imposed by their dimensions, is apparently achieved only by having two crystallographically different sets of succinimide molecules. Thus all four CO groups directed towards the tetraethylammonium ion are geometrically different although the nature of their attachment is the same. That a particular pair of substances, tetraethylammonium bromide and succinimide, should form an addition compound at all is seen to be dependent both on the distribution of charge in their components and on accidental and scarcely predictable dimensional factors.

The authors record their indebtedness to the late Professor E. A. Braude, who called their attention to this compound and provided a specimen. One of them (E. W.) thanks the Department of Scientific and Industrial Research for a Students' Maintenance Grant.

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SOUTH PARKS ROAD, OXFORD. [*Received, November 11th*, 1957.]

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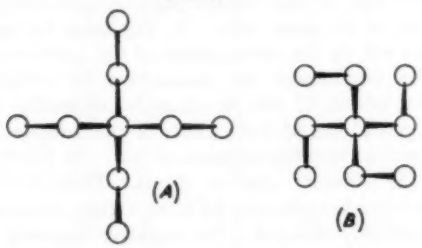
## 380. *The Crystal and Molecular Structure of Tetraethylammonium Iodide.*

By E. WAIT and H. M. POWELL.

Tetraethylammonium iodide forms a very distorted wurtzite-type structure, each ion having four neighbours of the opposite charge at the corners of a very flattened tetrahedron. The conformation of a tetraethylammonium ion is that which in projection forms a Nordic cross (swastika). Partly owing to steric effects the bond angle N–C–C is about 12° greater than the regular tetrahedral value.

ONLY two shapes, *A* and *B* (Fig. 1), are likely for the tetraethylammonium ion. Even in these conformations the distances between the carbon atoms of a terminal methyl and an adjacent methylene group would be less than 3 Å if the N–C–Me bond angle had the regular tetrahedral value, and the bonds the single covalent bond lengths. The normal contact distance between two such groups in neighbouring molecules is 4 Å.

FIG. 1.




Form *A* was found in the molecular compound of tetraethylammonium bromide with succinimide (preceding paper), but detailed examination of the bond distortion was not possible. The crystal structure of tetraethylammonium iodide has therefore been determined with a view to further examination of the form of the complex ion.

Crystals of tetraethylammonium iodide were examined goniometrically by Slavik,[1] who assigned them to the tetragonal class $\bar{4}2m$ and determined the axial ratio $c : a$ as 0·5544. Wyckoff [2] made an *X*-ray diffraction study and concluded that the iodine atoms

[1] Slavik, *Z. Kryst.*, 1902, **36**, 274.
[2] Wyckoff, *Z. Kryst.*, 1928, **67**, 550.

were in a body-centred array. On the morphological evidence he assumed the space-group to be one of those in the class $\bar{4}2m$. It is shown here that this assumption is incorrect and that the space-group is $I\bar{4}$. The assignment to a wrong crystal class was made because suitable faces did not develop. Unfortunately, it has led to this substance's being quoted as an example of the comparatively rare class $\bar{4}2m$.

Crystals suitable for *X*-ray work were obtained by recrystallisation of a commercial sample (B.D.H.) from hot water. Such a crystal had the form of a tetrahedron with smaller faces of a second tetrahedron truncating its corners (Slavik's Fig. 7). Filtered Cu-$K_\alpha$ radiation was used for the *X*-ray examination. Oscillation and zero- and first-layer equi-inclination Weissenberg photographs were taken for rotation about the *c* and *a* axes. They confirmed the tetragonal symmetry. The only systematically absent reflections were those with $h + k + l \neq 2n$. This corresponds to a body-centred lattice. Intensities of various classes of reflections showed the relationships $F_{hkl} = F_{\bar{h}\bar{k}\bar{l}}$; $F_{hkl} = F_{\bar{h}kl}$; $F_{hkl} = F_{h\bar{k}l}$; but $F_{hkl} \neq F_{k\bar{h}l}$. Since in all space-groups of the class $\bar{4}2m$, $F_{hkl} = F_{k\bar{h}l}$ it was concluded that the point symmetry was $\bar{4}$ and the space-group $I\bar{4}$. Cell dimensions from measurements of high-angle reflections on Weissenberg photographs calibrated with copper powder lines were $a = b = 8{\cdot}87 \pm 0{\cdot}02$ Å; $c = 6{\cdot}95 \pm 0{\cdot}02$ Å. They were in good agreement with the values given by Wyckoff. The density by flotation was $\rho = 1{\cdot}56 \pm 0{\cdot}01$ g./c.c. That calculated from cell dimensions on the assumption of two formula units $NEt_4I$ in the unit cell is 1·57 g./c.c. The intensities of 57 of the 61 independent $hk0$ reflections within the Cu-$K_\alpha$ sphere of reflection were measured on the *c* axis zero-layer Weissenberg photographs by visual comparison with a scale of spots of known intensity ratios prepared from the same crystal. From these, structure factors $F_{obs}$ were derived.

TABLE 1. *Observed and calculated structure factors.*

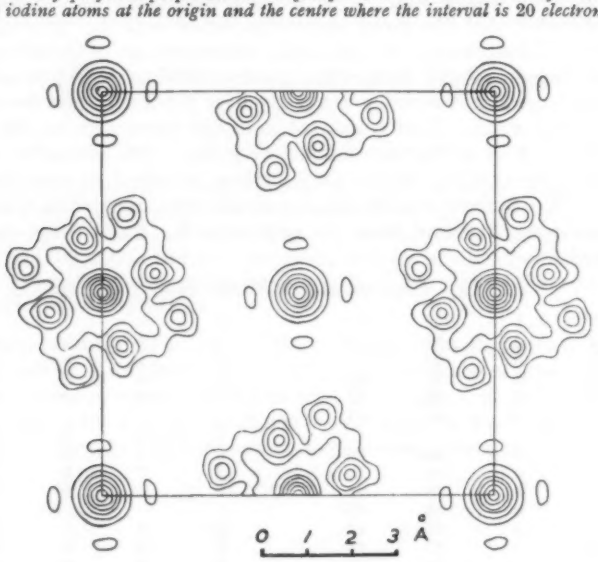
| *h* | *k* | *l* | $F_o$ | $F_c$ | *h* | *k* | *l* | $F_o$ | $F_c$ |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 0 | 0 | 118 | 114 | 4 | 2 | 0 | 65 | 65 |
| 4 | 0 | 0 | 65 | 78 | 4 | 6 | 0 | 52 | 48 |
| 6 | 0 | 0 | 51 | 60 | 4 | 8 | 0 | 28 | 26 |
| 8 | 0 | 0 | 26 | 34 | 4 | 10 | 0 | 14 | 18 |
| 10 | 0 | 0 | 18 | 18 | | | | | |
| | | | | | 5 | 1 | 0 | 50 | 60 |
| 1 | 1 | 0 | 44 | 38 | 5 | 3 | 0 | 54 | 46 |
| 2 | 2 | 0 | 72 | 74 | 5 | 7 | 0 | 23 | 22 |
| 3 | 3 | 0 | 79 | 74 | 5 | 9 | 0 | 22 | 22 |
| 4 | 4 | 0 | 50 | 55 | | | | | |
| 5 | 5 | 0 | 38 | 34 | 6 | 2 | 0 | 45 | 50 |
| 6 | 6 | 0 | 27 | 24 | 6 | 4 | 0 | 30 | 33 |
| 7 | 7 | 0 | 20 | 20 | 6 | 8 | 0 | 17 | 18 |
| 8 | 8 | 0 | 14 | 12 | | | | | |
| | | | | | 7 | 1 | 0 | 40 | 44 |
| 1 | 3 | 0 | 100 | 98 | 7 | 3 | 0 | 34 | 30 |
| 1 | 5 | 0 | 50 | 57 | 7 | 5 | 0 | 29 | 25 |
| 1 | 7 | 0 | 34 | 36 | | | | | |
| 1 | 9 | 0 | 25 | 25 | 8 | 2 | 0 | 34 | 37 |
| 1 | 11 | 0 | 14 | 18 | 8 | 4 | 0 | 31 | 32 |
| | | | | | 8 | 6 | 0 | 23 | 27 |
| 2 | 4 | 0 | 66 | 68 | | | | | |
| 2 | 6 | 0 | 62 | 75 | 9 | 1 | 0 | 24 | 25 |
| 2 | 8 | 0 | 36 | 40 | 9 | 3 | 0 | 12 | 11 |
| 2 | 10 | 0 | 21 | 22 | 9 | 5 | 0 | 12 | 14 |
| | | | | | | | | | |
| 3 | 1 | 0 | 66 | 81 | 10 | 2 | 0 | 22 | 25 |
| 3 | 5 | 0 | 34 | 33 | 10 | 4 | 0 | 22 | 26 |
| 3 | 7 | 0 | 18 | 18 | | | | | |
| 3 | 9 | 0 | 19 | 18 | 11 | 1 | 0 | 17 | 18 |

In the space-group $I\bar{4}$ there are four 2-fold special positions with co-ordinates (*a*) $\frac{1}{2}0\frac{1}{4}$, (*b*) $\frac{1}{2}0\frac{3}{4}$, (*c*) 000, (*d*) $00\frac{1}{2}$, and the corresponding body-centred co-ordinates. The point symmetry at each of these positions is $\bar{4}$. Since the *c* axis is comparatively short no structure can be formed in which one ion occupies (*a*) and the other (*b*). Similarly (*c*) and

(*d*) cannot both be used. The formally different ways of selecting one of (*a*) or (*b*) and one of (*c*) or (*d*) lead to structures which are identical apart from trivial interchange of axes or origin. The iodide ions may therefore be taken to be at 000 and $\frac{1}{2}\frac{1}{2}\frac{1}{2}$ and the nitrogen atoms at $0\frac{1}{2}\frac{1}{4}$ and $\frac{1}{2}0\frac{3}{4}$. The tetraethylammonium ion has a 4-fold axis of rotation inversion parallel to the *c* axis.

The projection of the structure on a plane perpendicular to *c* has a centre of symmetry, and the iodine atom at the origin makes its maximum possible positive contribution to each structure amplitude. This is almost equal to the total possible contribution from the remaining cell contents. It is therefore most probable that all $F_{hk0}$ will have positive signs. The Fourier F synthesis calculated with all signs taken as positive is shown in Fig. 2. All atoms except hydrogen are resolved. $F_{hk0}$ values were then calculated on the basis of the observed atomic co-ordinates. Scattering factors employed were those of

FIG. 2. *Electron density projected perpendicular to* [001]. *Contours at intervals of* 2 *electrons*/Å$^2$, *except for the iodine atoms at the origin and the centre where the interval is* 20 *electrons*/Å$^2$.




McWeeney [3] for carbon and nitrogen and of Thomas and Fermi [4] for iodine. All calculated structure amplitudes were positive. This confirms the initial assumption on which the F synthesis was based. The absolute scale of observed structure factors and an average temperature factor were determined from a plot of log $F_c'/F_o'$ against $\sin^2\theta$, where $F_c'$ is the structure factor calculated for atoms at rest and $F_o'$ the observed structure factor on an arbitrary scale. From the slope of the graph the value of the temperature factor was found as $B = 3{\cdot}1$ Å$^{-2}$. $F_o$ and $F_c$, the calculated structure amplitudes corrected for thermal vibration, are shown in Table 1. The discrepancy factor $R = \sum||F_o| - |F_c||/\sum|F_o|$ is 0·094. For comparison, the value of $R_I$, the discrepancy between the iodine contribution alone and $F_o$ reduced to the same scale, was $R_I = 0{\cdot}196$. The systematic errors in the atomic co-ordinates caused by termination of Fourier series at the limit of the sphere of reflection were now determined by Booth's "backshift" method.[5] The corrected co-ordinates are listed in Table 2. For the present purpose a 3-dimensional analysis which

[3] McWeeney, *Acta Cryst.*, 1951, **4**, 513.
[4] Internationale Tabellen zur Bestimmung von Krystallstrukturen, Band II, Borntraeger, Berlin, 1935.
[5] Booth, *Proc. Roy. Soc.*, 1946, *A*, **188**, 77.

would give the $z$ co-ordinates was not considered necessary since the information required could be deduced from the projection in the following way. The tetraethylammonium

TABLE 2. *Atomic co-ordinates.* (*For carbon atoms, values before application of backshift correction are shown in parentheses.*)

| | $x$ | $y$ | $z$ |
|---|---|---|---|
| I | 0 | 0 | 0 |
| N | $\frac{1}{2}$ | 0 | $\frac{1}{4}$ |
| $C_{(1)}$ | 0·367 (0·370) | 0·048 (0·047) | — |
| $C_{(2)}$ | 0·442 (0·442) | 0·190 (0·192) | — |

ion is seen directly to have form *B* (Fig. 1). If the inner carbon atoms are assumed to be at the vertices of a regular tetrahedron with the nitrogen at the centroid, then the N–C bond length is 1·49 Å, consistent with independently determined covalent radii. There is a geometrical relationship between the $X$ and $Y$ co-ordinates of the atoms as listed in Table 2, the $C_{(1)}$–$C_{(2)}$ bond length, and the N–$C_{(1)}$–$C_{(2)}$ bond angle. The variation in the bond angle for any probable values of the $C_{(1)}$–$C_{(2)}$ bond length $l$ was calculated. For $l = 1{\cdot}52$ the angle is 121° 9′ and as $l$ changes up to 1·57 the angle alters steadily to 121° 44′. It is concluded that the bond angle is approximately 12° greater than the regular tetrahedral angle. In contrast it has been reported that, in the crystal structure of tetra-*n*-propylammonium bromide,[6] the $CH_2$ groups of the complex ion adopt the conformation *A* (Fig. 1), the central N–C bond has length 1·55 ± 0·04 Å, and that an angle of 105° is found between two bonds of the nitrogen atom.

The general packing of the structure is determined largely by the size and shape of the tetraethylammonium ion. Fig. 3 shows that these ions are in contact with each other as well as with their iodine neighbours. There are no iodine–iodine contacts. The $a$ dimension is determined by the sum of the effective radii of the two ions, but contacts between tetraethylammonium ions alone are sufficient to fix $c$. As a result of this the arrangement is a very distorted form of the wurtzite (ZnS) type of structure, each ion being surrounded by four of the opposite kind located at the corners of a very flattened tetrahedron. Formally the wurtzite-type cubic unit cell is replaced by the tetragonal cell

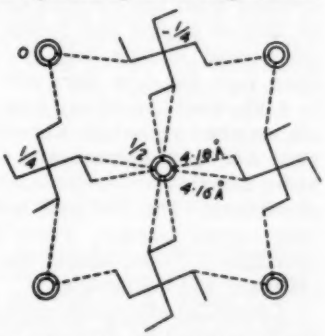



FIG. 3. *Projection of structure perpendicular to* [001].

Double circles = iodine. Co-ordinates along $c$ axis show for I and N. Tetraethylammonium ions indicated in skeletal form. Broken lines show contacts between iodine and the complex ion. Each methyl group at the corner of a Nordic cross is also at the contact distance of 3·92 Å from two methyl groups belonging to the complex ion immediately above or below, and located at the two neighbouring corners of the cross.

of height 6·95 Å and an $a$ dimension of 12·5 Å at 45° to the $a$ axis of the body-centred cell. The principal contact distances of Fig. 3 are consistent with known ionic and van der Waals radii for the relevant groups. The electrostatic attractions due to the iodide ions are applied to the positive ions in directions roughly perpendicular to the $\bar{4}$ axis in such a way that they might increase the deformation of the N–$C_{(1)}$–$C_{(2)}$ bond angle. Possibly this, as well as the repulsion between the over-crowded groups, may be a cause of the distortion.

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[*Received, November 11th*, 1957].

[6] Zalkin, *Acta Cryst.*, 1957, **10**, 557.

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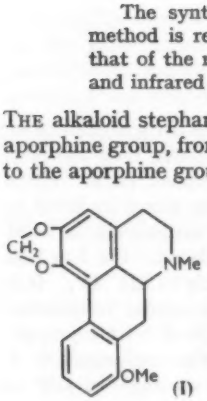
## 381. *The Aporphine Series. Part IV.* The Synthesis of (±)-Stephanine.*

By D. H. Hey and Ather Husain.

The synthesis of (±)-stephanine by the Bischler–Napieralski–Pschorr method is reported. The structural identity of the racemic product with that of the natural alkaloid is established by comparison of the ultraviolet and infrared absorption spectra of the two bases and their derivatives.

The alkaloid stephanine, $C_{19}H_{19}O_3N$, was isolated, together with related alkaloids of the aporphine group, from *Stephania capitata Spreng* by Tomita and Shirai.[1,2] It was assigned to the aporphine group on the basis of its ultraviolet absorption spectrum and was shown to contain one methoxyl group. The remaining two oxygen atoms were considered to be present as a methylenedioxy-group. Oxidation with permanganate gave 3-methoxyphthalic acid. Hofmann degradation followed by oxidation and decarboxylation gave a derivative of phenanthrene which was regarded as 1-methoxy-5 : 6-methylenedioxyphenanthrene. On the basis of these results the structure (I) was assigned to stephanine. As pointed out by Manske,[3] however, such a structure would be unusual in having a methoxyl group at position 1 in the aporphine system and seems from biogenetic considerations to be improbable. In order to obtain information for or against this structure the synthesis of (±)-stephanine was undertaken by the Bischler–Napieralski–Pschorr method.



(I)

The starting material, 2-methoxy-6-nitrophenylacetic acid, was prepared by Blaikie and Perkin,[4] from 2-hydroxy-6-nitrotoluene by methylation, condensation with ethyl oxalate, and oxidation of the resulting 2-methoxy-6-nitrophenylpyruvic acid. 2-Methoxy-6-nitrophenylacetic acid, erroneously described by them as a new compound, was later prepared by Cook, Loudon, and McCloskey [5] from 2-methoxy-6-nitrobenzyl cyanide, obtained from the corresponding benzyl chloride.[6] The method here used was based on that of Blaikie and Perkin. 2-Methoxy-6-nitrophenylacetic acid was converted in the normal manner into *N*-homopiperonyl-2-methoxy-6-nitrophenylacetamide, which when kept for eight days with phosphorus pentachloride in chloroform solution gave 3 : 4-dihydro-1-(2-methoxy-6-nitrobenzyl)-6 : 7-methylenedioxy*iso*quinoline, which was characterised as the hydrochloride, picrate, and methiodide. Reduction of the methiodide with zinc and hydrochloric acid gave 1-(2-amino-6-methoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinoline, which was characterised as the dipicrolonate. The free base, isolated from the dipicrolonate, was diazotised and treated with copper powder. From the resulting product 1-methoxy-5 : 6-methylenedioxyaporphine [(±)-stephanine] was isolated and characterised as the hydrochloride, chloroplatinate, and methiodide.

Ultraviolet absorption spectra were measured in 95% ethanol for natural stephanine, kindly supplied by Professor Tomita, and synthetic (±)-stephanine, as well as for their hydrochlorides and methiodides, and were found to be identical. In addition, infrared absorption spectra were measured in Nujol mulls for the two free bases and for their hydrochlorides and methiodides. So the structural identity of the two series of compounds was confirmed.

* Part III, *J.*, 1957, 2926.

[1] Tomita and Shirai, *J. Pharm. Soc. Japan*, 1942, **62**, 381.
[2] Shirai, *ibid.*, 1944, **64**, 44.
[3] Manske, "The Alkaloids," Academic Press Inc., New York, 1954, Vol. IV, p. 141.
[4] Blaikie and Perkin, *J.*, 1924, **125**, 312.
[5] Cook, Loudon, and McCloskey, *J.*, 1952, 3904.
[6] Buehler, Deebel, and Evans, *J. Org. Chem.*, 1941, **6**, 217.

After completion of this work it was learned that Shirai and Oda [7] had synthesised 1-methoxy-5 : 6-methylenedioxyphenanthrene and shown it to be identical with the compound obtained from stephanine by Hofmann degradation, followed by oxidation and decarboxylation, thus confirming the structure (I) for the alkaloid. Further, Tomita and Hirai [8] had synthesised (±)-1-methoxy-5 : 6-methylenedioxyaporphine and had shown it to be identical in structure with (−)-stephanine by a comparison of the ultraviolet absorption spectra of the methiodides. Tomita and Hirai used a different method for the preparation of their 2-methoxy-6-nitrophenylacetic acid and they obtained their *N*-homopiperonyl-2-methoxy-6-nitrophenylacetamide from the acid chloride and also directly from ω-diazo-2-methoxy-6-nitroacetophenone. The physical constants reported by Tomita and Hirai for their intermediates and derivatives are in good agreement with those recorded below. The synthetic work here reported is on several points more complete than that of Tomita and Hirai.

## Experimental

*2-Methoxy-6-nitrophenylacetic Acid.*—2 : 6-Dinitrotoluene was converted into 2-amino-6-nitrotoluene by Brady and Taylor's method [9] and thence into 2-hydroxy-6-nitrotoluene by Noelting's method.[10] Methylation by Ruggli and Leonhardt's method [11] gave 2-methoxy-6-nitrotoluene, which was converted into 2-methoxy-6-nitrophenylacetic acid, m. p. 170—171°, in 60% yield (Found: C, 51·5; H, 4·2. Calc. for $C_9H_9O_5N$: C, 51·2; H, 4·3%), as described by Blaikie and Perkin.[4]

*N-Homopiperonyl-2-methoxy-6-nitrophenylacetamide.*—A solution of homopiperonylamine (1·65 g.) in dry benzene (8 ml.) was added to a solution of 2-methoxy-6-nitrophenylacetyl chloride, prepared from the acid (2·1 g.) and thionyl chloride (5 ml.) in chloroform (10 ml.), in dry benzene (15 ml.). 10% Aqueous sodium hydroxide (10 ml.) was then added dropwise. The *amide*, which separated, was collected and crystallised from methanol in needles (3·2 g.), m. p. 157—158° (Found: C, 60·15; H, 5·1. $C_{18}H_{18}O_6N_2$ requires C, 60·3; H, 5·1%).

*3 : 4-Dihydro-1-(2-methoxy-6-nitrobenzyl)-6 : 7-methylenedioxyisoquinoline.*—The homopiperonylamide (2·0 g.) was finely powdered and added to well-cooled phosphorus pentachloride (2·0 g.) in dry chloroform (4 ml.). The closed flask was kept at room temperature for 8 days. The 3 : 4-dihydro*iso*quinoline hydrochloride which was deposited was collected and added at once to cold methanol (4 ml.). After 2 hr. the insoluble hydrochloride (1·4 g.; m. p. 172—174°) was collected. To a solution of the hydrochloride (2·65 g.) in ethanol (20 ml.) was added dilute ammonia solution (20 ml., *d* 0·96) dropwise with shaking. The free *base* which separated crystallised from benzene–light petroleum (b. p. 60—80°) in prismatic needles (2·20 g.), m. p. 148—149° (Found: C, 64·1; H, 4·9. $C_{18}H_{16}O_6N_2$ requires C, 63·5; H, 4·7%). The *picrate*, prepared in the normal manner, separated from ethanol in yellow needles, m. p. 214—215° (decomp.) (Found: C, 50·7; H, 3·9. $C_{18}H_{16}O_6N_2,C_6H_3O_7N_3$ requires C, 50·6; H, 3·4%). The *methiodide* separated from methanol in pale yellow flakes, m. p. 212—213° (decomp.) (Found: C, 47·0; H, 3·8. $C_{18}H_{16}O_6N_2,CH_3I$ requires C, 47·3; H, 3·9%).

*1-(2-Amino-6-methoxybenzyl)-1 : 2 : 3 : 4-tetrahydro-2-methyl-6 : 7-methylenedioxyisoquinoline.*—To an ice-cold suspension of the preceding methiodide (1·0 g.) in ethanol (30 ml.) was added concentrated hydrochloric acid (20 ml.) and then zinc dust (4·0 g.) during 10 min. After 30 min. more the mixture was heated on a boiling-water bath for 45 min. and then boiled under reflux for 15 min. The mixture was filtered, cooled in ice, and made alkaline with aqueous ammonia (*d* 0·88). The precipitate was washed twice with water, and the alkaline filtrate was extracted several times with ether. Evaporation of the dried ($Na_2SO_4$) ethereal extract left a residue to which a hot solution of picrolonic acid (2·0 g.) in ethanol (100 ml.) was added. In the cold the *dipicrolonate* (1·6 g.) separated, having m. p. 194—195° (decomp.) (Found: C, 54·1; H, 5·0. $C_{19}H_{22}O_3N_2,2C_{10}H_8O_5N_4,\frac{1}{2}H_2O$ requires C, 54·2; H, 4·5%).

*(±)-Stephanine* [*(±)-1-Methoxy-5 : 6-methylenedioxyaporphine*].—A suspension of the above

[7] Shirai and Oda, *J. Pharm. Soc. Japan*, 1956, **76**, 1287.
[8] Tomita and Hirai, *ibid.*, 1957, **77**, 290.
[9] Brady and Taylor, *J.*, 1920, **117**, 877.
[10] Noelting, *Ber.*, 1904, **37**, 1020.
[11] Ruggli and Leonhardt, *Helv. Chim. Acta*, 1924, **7**, 701.

XUM

dipicrolonate (2·5 g.) in cold methanol (10 ml.) was triturated with a cold mixture of concentrated sulphuric acid (2·5 ml.) and methanol (10 ml.). The picrolonic acid (1·45 g.), which separated, was filtered off and washed with methanol. To the combined filtrate and washings was added sodium nitrite (0·21 g.) in water (3·0 ml.) at −5° to 0°. After 10 hr. at 0° copper powder (0·5 g.) was added and a brisk evolution of nitrogen ensued. After being stirred for 30 min. the mixture was boiled under reflux for a similar period. The mixture was filtered and water (25 ml.) was added to the filtrate, followed by concentrated ammonia solution (*d* 0·88; 7·0 ml.). The mixture was then repeatedly extracted with ether (total volume 350 ml.), and the dried extract concentrated to about 5 ml. to which 15% hydrochloric acid (4·0 ml.) was added. The hydrochloride which separated was collected, dissolved in water (5·0 ml.), and extracted once with ether and several times with chloroform (total volume 150 ml.). Evaporation of the dried ($Na_2SO_4$) chloroform extract left (±)-stephanine hydrochloride, which crystallised from methanol–ether in needles (0·12 g.), m. p. 269—270° (decomp.) (Found: C, 65·35; H, 5·7. Calc. for $C_{19}H_{19}O_3N,HCl$: C, 66·0; H, 5·8%). (±)-Stephanine, liberated from the hydrochloride with ammonia in ethanol, crystallised from aqueous ethanol and then from benzene in needles, m. p. 131—133° (Found: C, 74·25; H, 6·1. Calc. for $C_{19}H_{19}O_3N$: C, 73·8; H, 6·2%). The *chloroplatinate* separated from ethanol in dull yellow needles, m. p. 220—222° (decomp.) (Found: Pt, 23·8. $C_{19}H_{19}O_3N,H_2PtCl_6,6H_2O$ requires Pt, 23·6%). The methiodide, prepared in the normal manner, had m. p. 221—222° (decomp.) (Found: C, 53·2; H, 5·2. Calc. for $C_{19}H_{19}O_3N,CH_3I$: C, 53·0; H, 4·9%). With Erdmann's reagent both the synthetic (±)-stephanine and natural (−)-stephanine gave a yellowish-orange colour; with Frohde's reagent both gave a yellowish-green colour.

The authors thank Professor Tomita, University of Kyoto, for a specimen of natural stephanine and for informing them of his completed synthesis of (±)-stephanine. Thanks are also accorded to the Ministry of Education, Government of Pakistan, for the award (to A. H.) of an Overseas Scholarship.

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## 382. *Homolytic Aromatic Substitution. Part XIII.* The Reaction of Benzoyl Peroxide with Naphthalene.*

By D. I. Davies, D. H. Hey, and Gareth H. Williams.

The decomposition of benzoyl peroxide in dilute solution in naphthalene at 85° and at 100° has been investigated. The main products have been found to be mixtures of the isomeric phenylnaphthalenes, naphthyl benzoates, and dinaphthyls, whose compositions have been measured by infrared spectroscopy. The results are discussed in terms of the mechanism of the various competing reactions and the relative reactivity of the 1- and the 2-position of the naphthalene nucleus towards attack by free radicals.

The reaction of naphthalene with aryl radicals from various sources has been studied by several groups of workers with confusing and, in some instances, conflicting results. Möhlau and Berger[1] found that naphthalene and benzenediazonium chloride in the presence of a little aluminium chloride yielded a mixture of 1- and 2-phenylnaphthalene containing about 90% of the 1-isomer; chlorobenzene was also found among the products. Huisgen and Sorge[2] studied the reaction of phenyl radicals derived from *N*-nitrosoacetanilide with a solution of naphthalene in benzene, and isolated a mixture of 1- and 2-phenylnaphthalene in 33% yield. The mixture was found to contain about 16% of the 2-isomer. Diphenyl was also obtained from these reactions, and was considered to be formed by the reaction of the phenyl radicals with benzene. From the relative amounts of diphenyl and 1- and 2-phenylnaphthalene isolated, naphthalene was estimated to be

* Part XII, *J.*, 1956, 1475.

[1] Möhlau and Berger, *Ber.*, 1893, **26**, 1196.
[2] Huisgen and Sorge, *Annalen*, 1950, **566**, 162.

22 times more reactive than benzene towards attack by phenyl radicals. Waters [3] studied the decomposition of benzenediazonium chloride in a solution of naphthalene in acetone, to which zinc dust was gradually added. 2-Phenylnaphthalene was isolated from the resulting mixture, and the presence of 1-phenylnaphthalene was inferred from the isolation of *o*-benzoylbenzoic acid from the products of oxidation of the mixture with chromic acid. Grieve and Hey [4] studied the reaction of *o*-carboxymethylphenyl radicals, derived from methyl anthranilate, with a solution of naphthalene in carbon tetrachloride. From the products, methyl *o*-α-naphthylbenzoate and a little methyl *o*-chlorobenzoate were isolated. Boyland and Sims [5] studied the reaction between equimolar quantities of benzoyl peroxide and naphthalene in chlorobenzene as solvent. Carbon dioxide, benzoic acid, and a mixture of 1- and 2-naphthyl benzoate were the only products identified. Dannley and Gippin,[6] who studied the reaction of benzoyl peroxide with various 1-substituted naphthalenes, were able to isolate only mixtures of esters. No products of phenylation were found. Lynch and Pausacker [7] investigated the reaction of benzoyl peroxide with naphthalene and isolated from the reaction mixture carbon dioxide, benzoic acid, 1- and 2-naphthyl benzoate (as 1- and 2-naphthol and benzoic acid after hydrolysis), 1- and 2-phenylnaphthalene, a high-boiling substance which was thought to be 1 : 4-diphenylnaphthalene, and an involatile residue of unspecified physical properties. In the most recent publication on the phenylation of naphthalene, Huisgen and Grashey [8] have described the phenylation of naphthalene in benzene solution by phenylazotriphenylmethane at 45°, by nitrosoacetanilide at 20—25°, and by benzoyl peroxide at 80°. From these reactions mixtures of 1- and 2-phenylnaphthalene containing approximately 80% of the 1- and 20% of the 2-isomer were isolated. From a competitive reaction with a mixture of naphthalene and pyridine with nitrosoacetanilide, it was found that naphthalene was phenylated 13 times more rapidly than pyridine. From a reaction between benzoyl peroxide and naphthalene a fraction, b. p. 210—280°/11 mm., was isolated, which crystallised in colourless leaflets. On crystallisation from benzene–ethanol, this material had m. p. 143—145° but, when the fused compound was allowed to solidify, it had m. p. 159°. The authors suggested that this compound is a diphenylnaphthalene. However, it is almost certainly 1 : 1′-dinaphthyl, since Orchin and Friedel [9] describe 1 : 1′-dinaphthyl as having these properties.

In the present work, which was completed before the publication of Lynch and Pausacker's and Huisgen and Grashey's papers, an attempt has been made partly to resolve the confusion which surrounds the reactions of naphthalene with free radicals by a detailed study of the relatively simple case of the decomposition of benzoyl peroxide in dilute solution in naphthalene. The formation of 1- and 2-phenylnaphthalene and 1- and 2-naphthyl benzoate has been confirmed, although at the lower temperature (85°) the yields are somewhat lower than might have been expected. In addition, the formation of 1 : 1′-, 2 : 2′-, and 1 : 2′-dinaphthyl, which have been found in the product to an appreciable extent (30—35%), is now reported for the first time. The discovery of the isomeric dinaphthyls in the product implies that Lynch and Pausacker's interpretation [7] of the stoicheiometry of the reaction must be regarded as incorrect. The proportions in which the isomeric phenylnaphthalenes, naphthyl benzoates, and dinaphthyls are formed have also been measured.

## Experimental

*Reagents.*—Benzoyl peroxide (from Messrs. May and Baker) was purified according to the procedure described in Part II.[10] *NN*-Dimethylformamide (from B.D.H.) was dried ($CaSO_4$)

[3] Waters, *J.*, 1939, 864.
[4] Grieve and Hey, *J.*, 1938, 108.
[5] Boyland and Sims, *J.*, 1953, 2966.
[6] Dannley and Gippin, *J. Amer. Chem. Soc.*, 1952, **74**, 332.
[7] Lynch and Pausacker, *Austral. J. Chem.*, 1957, **10**, 165.
[8] Huisgen and Grashey, *Annalen*, 1957, **607**, 46.
[9] Orchin and Friedel, *J. Amer. Chem. Soc.*, 1946, **68**, 573.
[10] Augood, Hey, and Williams, *J.*, 1952, 2094.

and distilled through a 25 cm. helix-packed column (b. p. 152°). Naphthalene (B.D.H.; May and Baker) was purified by crystallisation from ethanol to constant m. p. 80°. *cyclo*Hexane (May and Baker) was washed repeatedly with concentrated sulphuric acid, saturated sodium hydrogen carbonate solution, and water. After drying ($CaCl_2$) it was distilled through a 25 cm. helix-packed column (b. p. 81·6°/778 mm., $n_D^{16}$ 1·4286, m. p. 6·5°). *n*-Heptane (May and Baker) was shaken with concentrated sulphuric acid until the washings were colourless, then with water, then dilute potassium hydroxide, and finally water again until the washings were neutral to litmus. It was dried (KOH) and fractionally distilled, and the fraction of b. p. 98° was collected.

1-Phenylnaphthalene, prepared by the reaction of 1-naphthoyl peroxide with benzene, was distilled twice *in vacuo* (b. p. 117°/0·1 mm.). A specimen of 2-phenylnaphthalene prepared by Hey and Lawton [11] was crystallised from aqueous ethanol to constant m. p. 102°. 1- and 2-Naphthol (B.D.H.) were treated with activated charcoal in ethanol and crystallised to constant m. p. 96° and 123° respectively. 1- and 2-Naphthyl benzoate were crystallised from aqueous ethanol to constant m. p. 55° and 106° respectively. 1 : 1′-Dinaphthyl was prepared by an Ullmann reaction from 1-iodonaphthalene, and recrystallised from ethanol to constant m. p. 160° (Found: C, 94·4; H, 5·5. Calc. for $C_{20}H_{14}$: C, 94·45; H, 5·55%). Orchin and Friedel [9] report m. p. 145—147° and 159·5—160·5°. The present specimen of 1 : 1′-dinaphthyl showed no sign of melting in the region of 145° and melted only at 160°. When this form was recrystallised from benzene–ethanol it melted first at 144—146°, but subsequently solidified and re-melted at 159—160°. The infrared spectra in *cyclo*hexane solution of the single- and double-melting forms were identical, whereas the infrared spectra of Nujol mulls of the two forms showed differences. This peculiar behaviour of 1 : 1′-dinaphthyl is now under investigation. 1 : 2′-Dinaphthyl, prepared by Hooker and Fieser's method [12] from 2-bromonaphthalene and α-tetralone, was crystallised from light petroleum (b. p. 80—100°) to constant m. p. 75°. Hooker and Fieser [12] report m. p. 74·5—75°. 2 : 2′-Dinaphthyl was prepared by means of an Ullmann reaction, using 2-bromonaphthalene and copper bronze. It was obtained as white plates, m. p. 186—186·5° (Hooker and Fieser [12] report m. p. 185—186°) (Found: C, 94·4; H, 5·5. Calc. for $C_{20}H_{14}$: C, 94·45; H, 5·55%).

*Decomposition of Benzoyl Peroxide in Naphthalene.*—Experiment 1 was conducted with a relatively high concentration of benzoyl peroxide in order to identify the various products formed, and the results are therefore not quantitative. Benzoyl peroxide (15 g.) was allowed to decompose in naphthalene (100 g.) in a thermostat at 85° for 72 hr. In addition to free benzoic acid (9 g.) the following products were isolated by standard methods: (*a*) a pale yellow liquid (8 g.; b. p. 117—145°/0·1 mm.), which solidified and was shown to be a mixture of 1- and 2-phenylnaphthalene and 1- and 2-naphthyl benzoate by a comparison of its infrared spectrum with the spectra of authentic specimens of the four components; (*b*) 2 : 2′-dinaphthyl, m. p. and mixed m. p. 185—186·5° (Found: C, 94·6; H, 5·5%), whose ultraviolet spectrum was identical with that recorded in the literature [13] and whose infrared spectrum with that of an authentic specimen; and (*c*) a mixture of 1 : 1′- and 1 : 2′-dinaphthyl, from which the less soluble 1 : 1′-isomer, m. p. and mixed m. p. 158—160° (Found: C, 94·4; H, 5·6%), was obtained by crystallisation from dilute ethanol (cf. Smith [14]). The ultraviolet spectrum was identical with that recorded in the literature [13] and the infrared spectrum (*cyclo*hexane solution) was identical with that of a similar solution of authentic 1 : 1′-dinaphthyl.

Experiments 2—7 were carried out quantitatively, with benzoyl peroxide (5 g.) in naphthalene (150 g.), at 85° for 72 hr. (experiments 2—5) or at 100° for 24 hr. (experiments 6 and 7). When the decomposition was complete the reaction mixtures were diluted with benzene (400 ml.) and extracted exhaustively with saturated sodium hydrogen carbonate solution (10 × 50 ml.) to remove free benzoic acid. They were then worked up by the general procedure described in Part II,[10] except that 5N-sodium hydroxide was used to hydrolyse the esters and that the aqueous solution obtained from this hydrolysis was treated by standard methods for the isolation of 1- and 2-naphthol as well as benzoic acid. In the final distillation of the diaryl mixture at 0·1 mm., it was found that all the phenylnaphthalenes distilled below 140°, and that the dinaphthyls distilled at 160—200° at this pressure. The amount of involatile residue was extremely small. The results are given in Table 1.

[11] Hey and Lawton, *J.*, 1940, 374.
[12] Hooker and Fieser, *J. Amer. Chem. Soc.*, 1936, **58**, 1216.
[13] Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, New York, 1951.
[14] Smith, *J.*, 1877, **32**, 551.

Experiment 8 was conducted in order to determine whether any benzene is formed in the reaction. Benzoyl peroxide (5 g.) was allowed to decompose in naphthalene (150 g.) in a thermostat at 80° for 72 hr. The reaction flask was connected with a reflux condenser to prevent loss of benzene. Ten minutes before the flask was removed from the thermostat, *n*-heptane (50 ml.) was added to the mixture, so that on removal from the thermostat a homogeneous

TABLE 1.

| Experiment no.: | 2 | 3 | 4 | 5 | 6 | 7 * |
|---|---|---|---|---|---|---|
| Free benzoic acid (g.) | 2·79 | 2·83 | 2·85 | 2·82 | 2·49 | 2·48 |
| Naphthols (g.) | 0·95 | 0·96 | 0·93 | 0·94 | 0·70 | 0·73 |
| Benzoic acid from esters (g.) | 1·43 | 1·35 | 1·38 | 1·39 | 1·11 | 1·17 |
| Phenylnaphthalene fraction (g.) | 0·87 | 0·84 | 0·85 | 0·87 | 1·83 | 1·89 |
| Dinaphthyl fraction (g.) | 1·54 | 1·60 | 1·65 | 1·65 | 1·40 | 1·41 |
| High-boiling residue (g.) | 0·21 | 0·19 | 0·19 | 0·16 | 0·19 | 0·16 |
| Peroxide accounted for (%) | 94·0 | 92·9 | 94·0 | 93·8 | 93·1 | 94·8 |

* Experiments 2—5 at 85°, and 6 and 7 at 100°.

mixture was obtained. About 40 ml. of the solvent were then distilled out of the mixture through a 25 cm. helix-packed column. Any benzene formed in the reaction would be expected to co-distil with this *n*-heptane. The distillate was treated with a mixture of concentrated sulphuric acid (10 ml.) and fuming nitric acid (10 ml.) at room temperature. When addition of the mixed acids was complete the mixture was boiled under reflux for 15 min., and poured on ice (25 g.). The mixture was extracted with ether (5 × 40 ml.), and the extracts were washed repeatedly with water to remove all trace of acids, and finally dried ($Na_2SO_4$). The solvents were distilled off, leaving a small yellowish-brown residue which was dissolved in ethanol (10 ml.). This solution was poured into ice-water (50 ml.), and the residue removed by filtration. The residue (0·24 g.) was semi-solid and its infrared spectrum showed no correlation with that of *m*-dinitrobenzene. Thus it can be inferred that only very little, if any, benzene is formed in the reaction. When the *n*-heptane was distilled out of the mixture, a small amount of naphthalene sublimed with it, and it is probable that the semi-solid obtained on treatment with nitric acid was composed mainly of nitro-derivatives of naphthalene.

*Determination of Ratios of Isomers.*—The spectrographic analysis of the mixtures of phenylnaphthalenes, dinaphthyls, and naphthols obtained from reactions 2—7 was carried out with a Grubb-Parsons double-beam infrared spectrometer fitted with an automatic pen-recorder. For each analysis of a mixture of isomers the spectra of the pure isomers were first recorded in the range 2—15 μ, Nujol mulls between rock-salt plates being used in order to locate the " key bands " for the analysis. These were all found to lie in the range 12—14 μ, so that dimethylformamide and *cyclo*hexane were suitable solvents for all the analyses. The spectra of solutions of known concentration of the pure isomers and of the mixtures, in a 0·01″ rock-salt cell, were then recorded. The calculations of the composition of the mixtures from the infrared spectra were carried out as described in Part III.[15]

(i) *Naphthols.* Dimethylformamide was used as solvent and measurements were made at the following characteristic absorption maxima: 1-naphthol, 12·52 μ, 2-naphthol, 13·26 μ. The weights of the two components were calculated directly. The accuracy of the method was tested by the analysis of two synthetic mixtures (A) and (B) of known composition. These

TABLE 2. *Analyses of mixtures of known composition.*

| | Naphthols | | | | | Phenylnaphthalenes | | | | | Dinaphthyls | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Known (%) | | Found (%) | | | Known (%) | | Found (%) | | | Known (%) | | Found (%) | | |
| | 1- | 2- | 1- | 2- | | 1- | 2- | 1- | 2- | | 1 : 1′- | 1 : 2′- | 1 : 1′- | 1 : 2′- | |
| A | 59·2 | 40·8 | 59·2 | 40·8 | C | 79·6 | 20·4 | 80·2 | 19·8 | E | 29·4 | 70·6 | 30·4 | 69·6 | |
| B | 75·1 | 24·9 | 74·7 | 25·3 | D | 77·0 | 23·0 | 76·9 | 23·1 | F | 58·7 | 41·3 | 58·6 | 41·4 | |

results are given in Table 2. The results of the analysis of the mixtures obtained from experiments 2—7 are given in Table 3. The purity of the naphthol mixtures is indicated by the sum of the weights of the two components as determined by the analysis, which in all the experiments is not less than 97% of the weight of the original naphthol mixture taken. The data given in Tables 2 and 3 were calculated by expressing the weight of each component in turn as a percentage of the sum of the determined weights of both components.

[15] Augood, Hey, and Williams, *J.*, 1953, 44.

(ii) *Phenylnaphthalenes.* The reaction mixture was twice redistilled at 0·1 mm. to ensure removal of any dinaphthyls. The product was a pale yellow liquid which partly solidified. *cyclo*Hexane was used as solvent and measurements were made at the following characteristic absorption maxima: 1-phenylnaphthalene, 12·48 μ; 2-phenylnaphthalene, 12·22 μ. The accuracy of the determination was tested by the analysis of synthetic mixtures (C) and (D) of

TABLE 3. *Products obtained from the reactions of benzoyl peroxide with naphthalene.*

| Expt. no. | Naphthols (%) | | Phenylnaphthalenes (%) | | 2 : 2′-Dinaphthyl (g.) | 1 : 1′- and 1 : 2′-Dinaphthyls (%) | | Total dinaphthyls (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1- | 2- | 1- | 2- | | 1 : 1′- | 1 : 2′- | 1 : 1′- | 1 : 2′- | 2 : 2′- |
| 2 | 73·9 | 26·1 | 82·2 | 17·8 | 0·064 | 56 | 44 | 54 | 42 | 4 |
| 3 | 72·7 | 27·3 | 83·1 | 16·9 | 0·064 | 57 | 43 | 55 | 41 | 4 |
| 4 | 72·2 | 27·8 | 82·3 | 17·7 | 0·066 | 56 | 44 | 54 | 42 | 4 |
| 5 | 72·7 | 27·3 | 80·5 | 19·5 | 0·065 | 55 | 45 | 53 | 43 | 4 |
| 6 | 68·9 | 31·1 | 80·0 | 20·0 | 0·043 | 56 | 44 | 54 | 42 | 4 |
| 7 | 67·4 | 32·6 | 79·4 | 20·6 | 0·041 | 56 | 44 | 54 | 43 | 3 |

known composition (Table 2). The method of calculation employed was similar to that used in the analysis of the mixtures of 1- and 2-naphthol. The sum of the weights of the two components as determined in the analysis was, in all the experiments, not less than 99% of the weight of the phenylnaphthalene mixture taken. The results of the analysis of the mixtures obtained from experiments 2—7 are given in Table 3.

(iii) *Dinaphthyls.* The dinaphthyl fraction was digested with light petroleum (b. p. 80—100° 20 ml.), and the resulting solution allowed to cool. Pale yellow crystals of 2 : 2′-dinaphthyl were deposited and were removed by filtration (m. p. and mixed m. p. 182—184°). The weights of 2 : 2′-dinaphthyl obtained in experiments 2—7 are given in Table 3. The filtrate, after removal of 2 : 2′-dinaphthyl, was transferred to a small flask packed with glass wool, and the light petroleum was removed by distillation at atmospheric pressure. The dinaphthyls distilled at 0·1 mm. as a pale yellow viscous liquid which solidified, and this product was used for isomer analysis of 1 : 1′- and 1 : 2′-dinaphthyl.

1 : 2′-Dinaphthyl has absorption maxima of medium intensity at 12·17 and 13·42 μ. At these wavelengths the absorption due to 1 : 1′-dinaphthyl is negligible. The analysis of the mixtures of 1 : 1′- and 1 : 2′-dinaphthyl for 1 : 2′-dinaphthyl by measuring the intensity of absorption of mixtures in *cyclo*hexane at these wavelengths was carried out. The amounts of 1 : 1′-dinaphthyl were obtained by difference. The accuracy of the method was estimated by analysis of mixtures (E) and (F) of known composition (Table 2).

The spectra of mixtures from experiments 2—7 in solution in *cyclo*hexane contained a band of very weak intensity at 13·13 μ which was not present in the spectra of either 1 : 1′- or 1 : 2′-dinaphthyl. Also, the intensity of the absorption band at 13·42 μ was slightly greater than that expected when the percentage of 1 : 2′-dinaphthyl in the mixtures was calculated on the basis of the intensity of absorption at 12·17 μ. Thus it appears that the dinaphthyl fractions contained a small amount of extraneous material, possibly diphenylnaphthalenes. It is, of course, conceivable that this extraneous material is 2 : 2′-dinaphthyl. This is, however, considered unlikely, since the solubility of 2 : 2′-dinaphthyl in *cyclo*hexane at room temperature is extremely low and, moreover, a saturated solution of 2 : 2′-dinaphthyl in *cyclo*hexane showed negligible absorption at this wavelength. Likewise, the spectrum of 2 : 2′-dinaphthyl as a mull in Nujol showed negligible absorption at 13·13 μ. The intensity of the band at 13·13 μ was greater in spectra of mixtures from reactions at 100° than from those at 85°, and it was estimated that the dinaphthyl mixtures from reactions at 85° and 100° contained approximately 5% and 15%, respectively, of the extraneous material. Taking this into account, we obtained isomer ratios by using the absorption maximum at 12·17 μ and assuming the absorption due to the extraneous material to be small at this wavelength (Table 3). Taking into account the 2 : 2′-dinaphthyl already isolated, we obtained figures (Table 3) for the proportions of the isomeric dinaphthyls in the original mixtures.

## DISCUSSION

The results reported in this communication are summarised in Tables 4, 5, and 6. The mean molar yields of the various products of the reaction at the two temperatures at which it was investigated are given in Table 4.

The mean percentage compositions of the mixtures of isomeric naphthols and phenylnaphthalenes at the two temperatures are given in Table 5, and those of the mixtures of of dinaphthyls in Table 6.

TABLE 4.

| Product | Mean yield (moles/mole benzoyl peroxide) 85° | 100° |
|---|---|---|
| Free benzoic acid | 1·12 | 0·99 |
| Naphthols | 0·32 | 0·24 |
| Benzoic acid from esters | 0·55 | 0·45 |
| Phenylnaphthalenes | 0·20 | 0·44 |
| Dinaphthyls * | 0·29 | 0·23 |
| Peroxide not accounted for | 0·06 | 0·06 |

* Calc. on the basis that the dinaphthyl fraction at 85° contains 95% of dinaphthyls and at 100° 85% of dinaphthyls.

TABLE 5.

| | Mean composition (%) 1- | 2- | | Mean composition (%) 1- | 2- |
|---|---|---|---|---|---|
| Naphthols (85°) | 72·9 | 27·1 | Phenylnaphthalenes (85°) | 82·0 | 18·0 |
| ,, (100°) | 68·2 | 31·8 | ,, (100°) | 79·7 | 20·3 |

TABLE 6.

| | Mean percentage composition 1 : 1′- | 1 : 2′- | 2 : 2′- |
|---|---|---|---|
| Dinaphthyls (85°) | 54 | 42 | 4 |
| ,, (100°) | 54 | 42 | 4 |

The major hydrocarbon products of the reaction are seen to be phenylnaphthalenes and dinaphthyls. Very little polyphenylation, which would yield, for example, diphenylnaphthalenes, was found. This contention is supported by the observation that the free benzoic acid isolated was pure, as indicated by its melting point, and contained little or no diphenylcarboxylic acids. This is in contrast to the situation which obtains when further phenylation of the primary reaction products takes place to an appreciable extent, diphenylcarboxylic acids, arising from phenylation of the benzoic acid formed as a primary product, being then formed and sometimes isolated (see, for example, Hey, Pengilly, and Williams [16]). The product which was isolated and thought to be 1 : 4-diphenylnaphthalene by Lynch and Pausacker [7] is almost certainly a mixture of dinaphthyls, which these authors did not identify as reaction products. The appreciable amount of high-boiling residue found by these workers may also consist largely of dinaphthyls, which would probably be involatile under the conditions of Lynch and Pausacker's final distillation. The absence of polyphenylation products in this reaction is consistent with the high reactivity of naphthalene towards attack by phenyl radicals (Huisgen and Sorge [2]). This point has also been discussed by Augood and Williams,[17] who pointed out that the formation of polyphenylation products was inconsistent with the high reactivity of naphthalene. This anomaly is now resolved by the demonstration that the high-boiling material consists of dinaphthyls, very little, if any, polyphenylnaphthalenes being formed.

The phenylnaphthalenes are undoubtedly formed by direct phenylation of naphthalene by phenyl radicals derived from the benzoyl peroxide. The proportions in which the 1- and the 2-isomers are formed demonstrate the greater reactivity of the 1-position to free-radical attack, and are in this respect in accord with the predictions of theoretical treatments depending on the calculation of free-valence numbers [18] and of atom localisation energies.[19]

[16] Hey, Pengilly, and Williams, *J.*, 1955, 6.
[17] Augood and Williams, *Chem. Rev.*, 1957, **57**, 123.
[18] Sandorfy, *Bull. Soc. chim. France*, 1949, **16**, 615; Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553; Coulson and Longuet-Higgins, *Rev. Sci.*, 1947, **85**, 929; Coulson, *J. Chim. phys.*, 1948, **45**, 243.
[19] Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900.

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The formation of the isomeric dinaphthyls is believed to be due to the abstraction of hydrogen from the nucleus of naphthalene to give 1- and 2-naphthyl radicals, which in turn attack the solvent naphthalene in much the same way as phenyl radicals. This process results in the formation of all three dinaphthyls, since both 1- and 2-naphthyl radicals are capable of effecting substitution at the 1- and the 2-position of naphthalene. The proportions in which the isomeric dinaphthyls are formed ($1:1'- > 1:2'- > 2:2'-$) are consistent with the reasonable assumptions (*a*) that for hydrogen-abstraction, as for substitution, the 1-position is the more reactive, and therefore that more 1- than 2-naphthyl radicals are formed, and (*b*) that the order of reactivity of the 1- and the 2-position in naphthalene (1- > 2-) is the same for naphthylation as for phenylation, so that substitution by both 1- and 2-naphthyl radicals takes place more readily at the 1-position. The radical responsible for the initial abstraction of hydrogen from the naphthalene nucleus is thought to be benzoyloxy rather than phenyl, on account of the failure to identify benzene among the products, since benzene must be formed if phenyl radicals participate in the hydrogen-abstraction. The participation of the benzoyloxy- rather than the phenyl radical in this reaction is probably due to the high reactivity of the naphthalene nucleus towards free-radical attack. Consequently it appears that direct reaction of the normally unstable benzoyloxy-radicals becomes a sufficiently advantageous reaction path to allow it to compete with the more usual processes of decarboxylation and subsequent reaction of the resulting phenyl radicals. The benzoyloxy-radicals react with naphthalene in two ways, namely, by hydrogen-abstraction, to give naphthyl radicals and ultimately dinaphthyls, and by direct substitution to give naphthyl benzoates. Since, as established above, phenyl radicals do not react with naphthalene by hydrogen abstraction, in contrast with benzoyloxy-radicals, it is obvious that the alternative reaction of direct substitution is energetically favoured in this case. The source of this energetic advantage is probably the extra resonance energy associated with the formation of a diaryl, which results in a measure of stabilisation of the transition state and consequent lowering of the activation energy for substitution relative to hydrogen-abstraction by phenyl radicals, as compared with the corresponding quantities for substitution and hydrogen-abstraction by benzoyloxy-radicals. The inability of phenyl radicals to react with naphthalene by hydrogen-abstraction is also demonstrated by the fact that dinaphthyls do not appear to be formed when sources of phenyl radicals are used which do not involve the intermediation of benzoyloxy-radicals.[1,2]

As implied in the foregoing discussion, the naphthyl benzoates are formed most probably by direct substitution in the naphthalene nucleus by benzoyloxy-radicals. The proportion in which the 1- and the 2-isomers are formed is given by the proportion in which 1- and 2-naphthol occur in their hydrolysis product, and it may be seen from Table 5 that while the 1-position is still the more reactive, more substitution in the 2-position takes place in benzoyloxylation than in phenylation. This difference may be due to the difference in polar character of the benzoyloxy- and the phenyl radical, or to steric difficulty of substitution by the benzoyloxy-radical in the 1-position, or to a combination of both factors. The experimental evidence is at present insufficient to permit further profitable discussion of these effects and of other possible modes of formation of the naphthyl benzoates, which may include, for instance, the reaction between naphthyl radicals and benzoyl peroxide. The experimental results show that for both benzoyloxylation and phenylation of naphthalene the amount of the 2-isomer increases slightly with rise in temperature. This is in accordance with most other substitution reactions in which isomer distribution becomes more nearly statistical as the temperature is raised. The extent of arylation of naphthalene by phenyl radicals from benzoyl peroxide increases markedly as the reaction temperature is increased. This is presumably a result of easier decarboxylation of the benzoyloxy-radicals at higher temperatures. Consequently, the extent of substitution in naphthalene by benzoyloxy-radicals to give naphthyl benzoates decreases as the temperature is raised, and this is amply demonstrated by the experimental results.

In addition to the results presented in this paper we have investigated the reactions of di-*o*-, -*m*-, and -*p*-nitrobenzoyl peroxides with naphthalene. The main product in each case is a mixture of naphthyl nitrobenzoates, accompanied by a relatively small quantity of a mixture of dinaphthyls. No arylation of naphthalene takes place with any of these reagents. These and other results on the homolytic reactions of naphthalene will be presented in future papers.

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## 383. *Homolytic Aromatic Substitution. Part XIV.* Ratio of Isomerides Formed in the Arylation of Nitrobenzene with* p-*Chlorophenyl and* p-*Bromophenyl Radicals.*

By CHANG SHIH, D. H. HEY, and GARETH H. WILLIAMS.

Measurements are reported of the ratios of isomers obtained in the arylation of nitrobenzene with *p*-chlorophenyl and *p*-bromophenyl radicals. The measurements for *p*-chlorophenylation were made by the infrared spectrographic method, and those for *p*-bromophenylation by the infrared and the isotope-dilution methods. The agreement between the results obtained by the two methods is satisfactory. In order to confirm earlier results, and for comparison, the ratio of isomers obtained in the phenylation of nitrobenzene was measured by the ultraviolet-spectrophotometric method. The results show that the slightly electrophilic nature of the halogen-substituted radical gives rise to a small increase in the proportion of the *meta*-substituted isomer when it reacts with nitrobenzene.

IN Part IX [1] competitive experiments on the arylation of chlorobenzene and nitrobenzene with *p*-chlorophenyl radicals were described, whereby the relative rates of *p*-chlorophenylation of nitrobenzene (${}^{PhNO_2}_{PhH}K$) and chlorobenzene (${}^{PhCl}_{PhH}K$) were measured. From these results it was apparent that both relative rate ratios were significantly lower than the corresponding quantities for phenylation of these compounds, and in explanation it was suggested that, as a result of the inductive ($-I$) effect of the chlorine atom, the probability of localisation of the unpaired electron at the *para*-position of the radical is reduced. The *p*-chlorophenyl radical was therefore considered to assume some measure of electrophilic character, and since both nitrobenzene and chlorobenzene are deactivated towards electrophilic substitution, it is to be expected that a decrease should be observed in the relative rates of arylation of these compounds as more electrophilic radicals are used. Changes, due to the presence of substituent groups in the radicals, in the ratios of isomers formed in the arylation of various compounds have been reported by DeTar and Kazimi,[2] Dannley and Sternfeld,[3] and Simamura and Migita.[4] These changes are consistent with the above hypothesis. In order further to establish its validity a systematic study of the arylation of a number of selected compounds with substituted radicals containing substituents of various polar characteristics, was undertaken, the results being reported in this and subsequent papers.

* Part XIII, preceding paper.

[1] Cadogan, Hey, and Williams, *J.*, 1955, 1425.
[2] DeTar and Kazimi, *J. Amer. Chem. Soc.*, 1955, **77**, 3842.
[3] Dannley and Sternfeld, *ibid.*, 1954, **76**, 4543.
[4] Simamura and Migita, *Bull. Chem. Soc. Japan*, 1954, **27**, 228.



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In this paper, measurements of the ratios of isomers produced in the *p*-chlorophenylation and *p*-bromophenylation of nitrobenzene at 80° are reported. The mixtures of chloronitrodiphenyls were analysed by infrared spectroscopy, and mixtures of bromonitrodiphenyls by both infrared spectroscopy and the isotope-dilution method. The agreement between the results obtained by the two methods is good, and is a measure of the accuracy of the determinations. Theoretical interpretation of these results involves their comparison with the ratio of isomers formed in the phenylation of nitrobenzene. This ratio has been measured for the reaction at 80° by Hey, Nechvatal, and Robinson (Part I) [5], by the infrared method. The two mixtures analysed by these workers had the following compositions: *ortho* 59·5 ± 4 and 59·5 ± 4, *meta* 8·5 ± 2 and 11·5 ± 2, *para* 32 ± 4 and 29 ± 4%. However, it is apparent from the infrared absorption spectra of 2-, 3-, and 4-nitrodiphenyl that some overlapping of the absorption bands of the three isomers occurs, and therefore that the accuracy of the infrared method is somewhat diminished in this system. The ratio of isomers for this reaction at 125° has been measured by Hey, Stirling, and Williams (Part VI),[6] who showed that good results could be obtained by ultraviolet spectrophotometry. Owing to the difference in temperature, however, these measurements are not suitable for comparison with the measurements presently reported, and hence it was considered desirable to repeat the determination of the ratio of isomers obtained in the phenylation of nitrobenzene at 80°, using the ultraviolet method for the analysis. This desirability becomes of greater significance in view of the small differences, only just outside the experimental error of the determinations, which are expected between the isomer ratios displayed by the unsubstituted and substituted phenyl radicals. The results are summarised in Table 1. The results for *p*-bromophenylation may be compared with those of Hey, Nechvatal, and Robinson [5] who found, as a result of a volumetric analysis, that such reactions gave rise to about 12% of the *meta*-isomer.

TABLE 1. *Ratios of isomers obtained in the arylation of nitrobenzene* (80°).

| Radical | Composition of diaryl (%) 2- | 3- | 4- |
|---|---|---|---|
| $C_6H_5$ | 62·5 | 9·8 | 27·7 |
| *p*-Cl·$C_6H_4$ | 59·0 | 13·8 | 27·2 |
| *p*-Br·$C_6H_4$ * | 57·7 | 13·2 | 29·1 |

* Mean of results obtained by infrared and isotope-dilution methods.

The influence of the electrophilic or nucleophilic character of the radicals is made apparent most clearly by the amount of substitution at the *meta*-position, since electrophilic radicals should give rise to an increased, and nucleophilic radicals a decreased amount of *meta*-substitution when they react with a compound such as nitrobenzene containing a directing group which is deactivating, and *meta*-directing towards electrophilic substitution. It may be seen from Table 1, therefore, that *p*-chlorophenyl and *p*-bromophenyl radicals are both slightly electrophilic, since both give rise to a small increase in the amount of *meta*-substitution. The differences are small, but in view of the special precautions taken to confirm the values obtained for phenylation and *p*-bromophenylation, the effects they illustrate are accepted as real, at least in a qualitative sense. These results, together with others reported in subsequent papers, will be further discussed in a later paper.

## EXPERIMENTAL

*Preparation of Reagents.*—Unless otherwise stated, the light petroleum used had b. p. 60—80°, and solids were recrystallised to constant m. p.

[5] Hey, Nechvatal, and Robinson, *J.*, 1951, 2892.
[6] Hey, Stirling, and Williams, *J.*, 1954, 2747.

Benzoyl peroxide (May and Baker) and nitrobenzene were purified according to the procedures described in Part II,[7] and nitromethane according to that described in Part IV.[8]

*p*-Bromobenzoyl peroxide (m. p. 142°) and *p*-chlorobenzoyl peroxide (m. p. 138°) were prepared by Hey and Walker's method.[9] 2-Nitrodiphenyl (m. p. 35—36°) and 4-nitrodiphenyl (m. p. 114°) were prepared by Bell, Kenyon, and Robinson's method.[10] 2-Nitrodiphenyl was further purified by repeated fractional distillation *in vacuo*. 3-Nitrodiphenyl was prepared by Hey and Walker's method [9] (m. p. 61°) and by Elks, Haworth, and Hey's method [11] (m. p. 60°).

4-*Chloro-2′-nitrodiphenyl* was prepared by direct chlorination of 2-nitrodiphenyl. Dry chlorine was passed into a mixture of 2-nitrodiphenyl (10 g.) and stannic iodide (0·5 g.) at 40° until the gain in weight was 2 g. The rate of flow of chlorine, and the temperature at which the reaction was carried out, were found to be critical, and consequently the rate of flow of chlorine was controlled by a simple flow-meter adjusted to about 0·5 ml. per second. The product, after repeated crystallisation from methanol, and chromatography on alumina with chloroform as eluent, was obtained as yellow prisms, m. p. 61° (1·9 g.) (Found: Cl, 14·7. $C_{12}H_8O_2NCl$ requires Cl, 15·2%).

4-Chloro-3′-nitrodiphenyl (m. p. 89°) was prepared by Blakey and Scarborough's method [12] by chlorination of 3-nitrodiphenyl at 80° in the presence of ferric chloride. 4-Chloro-4′-nitrodiphenyl (m. p. 158°) was prepared by Le Fèvre and Turner's method,[13] chlorination of 4-nitrodiphenyl at a temperature just above its m. p. in the presence of a little stannic iodide.

For the preparation of 4-bromo-2′-nitrodiphenyl, Le Fèvre and Turner's method [13] was first used, but it was found that the yield was poor, and the isolation of the product troublesome. The following modified procedure was, however, found to be satisfactory. 2-Nitrodiphenyl was first carefully purified by repeated fractional distillation *in vacuo* and repeated crystallisation from ethanol. Traces of 4-nitrodiphenyl, with which the 2-isomer is usually contaminated, were thus removed. In this way, isolation of the final product was greatly facilitated, since contamination with bromo-derivatives of 4-nitrodiphenyl was avoided. A mixture of this purified 2-nitrodiphenyl (9 g.), bromine (3·2 ml.), ferric chloride (0·4 g.), and water (10 ml.) was stirred overnight at room temperature. The mixture was then stirred with an excess of 5% sodium carbonate solution and extracted with ether. The ethereal extract was washed with 5% aqueous sodium carbonate and, after being dried ($K_2CO_3$), the ether was removed by evaporation. The residue was crystallised repeatedly from ethanol, and final purification by chromatography yielded 4-bromo-2′-nitrodiphenyl as yellow plates, m. p. 66° (3·2 g.). This represents a yield of 25%, and is a considerable improvement on Hey, Nechvatal, and Robinson's method,[5] which gave only 10%. Le Fèvre and Turner [13] recorded neither yield nor m. p., but Schultz, Schmidt, and Strasser [14] recorded m. p. 65°.

4-Bromo-3′-nitrodiphenyl (m. p. 94°) was obtained by bromination of 3-nitrodiphenyl as described by Blakey and Scarborough,[12] and 4-bromo-4′-nitrodiphenyl (m. p. 176°) similarly by Le Fèvre and Turner's method.[13]

The preparation of $^{82}$Br-labelled 4-bromo-4′-nitrodiphenyl and 4-bromo-2′-nitrodiphenyl, which were required for the isotope-dilution analyses, was carried out by using radioactive $^{82}$Br supplied by the United Kingdom Atomic Energy Research Establishment, Harwell.

4-[$^{82}$Br]*Bromo-4′-nitrodiphenyl*.—Pure 4-nitrodiphenyl (2 g.), acetic acid (4·6 ml.), and radioactive bromine (1 ml.) were heated together for 4 hr. on a water-bath. The mixture was then cooled, and filtered, and the residue washed with a little acetic acid. After crystallisation from glacial acetic acid (3 times) the pure compound was obtained as pale yellow needles, m. p. 176° (1·9 g.).

4-[$^{82}$Br]*Bromo-2′-nitrodiphenyl*.—Pure 2-nitrodiphenyl (5·6 g.), water (6 ml.), ferric chloride (0·2 g.), and active bromine (2 ml.) were stirred overnight at room temperature. The product was isolated by the procedure previously described for the preparation of the inactive material, giving bright yellow needles, m. p. 65° (2 g.).

[7] Augood, Hey, and Williams, *J.*, 1952, 2094.
[8] Augood, Cadogan, Hey, and Williams, *J.*, 1953, 3412.
[9] Hey and Walker, *J.*, 1948, 2216.
[10] Bell, Kenyon, and Robinson, *J.*, 1926, 1243.
[11] Elks, Haworth, and Hey, *J.*, 1940, 1285.
[12] Blakey and Scarborough, *J.*, 1927, 3003.
[13] Le Fèvre and Turner, *J.*, 1928, 253.
[14] Schultz, Schmidt, and Strasser, *Annalen*, 1881, **207**, 351.

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*Reaction of* p-*Chlorobenzoyl Peroxide with Nitrobenzene.*—In experiments 1 and 2, *p*-chlorobenzoyl peroxide (6 g.) was allowed to decompose in nitrobenzene (200 ml.) in a thermostat at 80° for 72 hr. The diaryl fraction containing the isomeric 4-chloronitrodiphenyls was obtained as a pale yellow solid (b. p. 55—130°/0·1 mm.) from the dark brown reaction mixture by standard methods (cf. Part II [7]). The yields of diaryls from these two experiments were 3·725 and 3·667 g. respectively. No high-boiling resins were formed, and the diaryl fractions were shown by spectrographic analysis to contain no extraneous material.

*Reaction of* p-*Bromobenzoyl Peroxide with Nitrobenzene.*—Experiments 3 and 4 were conducted with 6 g., and experiments 5 and 6 with 9 g., of *p*-bromobenzoyl peroxide in nitrobenzene (200 ml.). The diaryl fractions were isolated as above (b. p. 55—135°/0·1 mm.), and shown by spectrography to contain no extraneous material. No high-boiling resins were formed. The yields of diaryl were 3·075, 2·984, 4·764, and 4·465 g. respectively. The products of experiments 3 and 4 were analysed spectrographically, and those of experiments 5 and 6 by the isotope-dilution method.

*Reaction of Benzoyl Peroxide with Nitrobenzene.*—In experiments 7 and 8, benzoyl peroxide (3 g.) was allowed to decompose in nitrobenzene (100 ml.) at 80° for 72 hr. The mixtures of diaryls were obtained as yellow oils (b. p. 90—125°/0·2 mm.). The yields were 1·947 and 1·987 g. respectively, only a small amount of high-boiling resinous material being obtained. The diaryl fractions were shown by spectrographic analysis to contain no extraneous material.

*Analysis of Mixtures of Isomers by the Infrared Method.*—The instrument used was a Grubb-Parsons single-beam spectrometer fitted with an automatic pen-recorder. Nitromethane was used as solvent, since it has only one intense absorption band in the region 700—900 cm.$^{-1}$, in which the characteristic bands of the relevant diaryls fall, and this band does not coincide with any of the characteristic diaryl bands. Calibration spectra were recorded for the isomeric 4-chloronitrodiphenyls and 4-bromonitrodiphenyls, and measurements on the spectra of mixtures for analysis made at the following characteristic absorption maxima: 4-chloro-2′-nitrodiphenyl, 788 cm.$^{-1}$; 4-chloro-3′-nitrodiphenyl, 811 cm.$^{-1}$; 4-bromo-2′-nitrodiphenyl, 784 cm.$^{-1}$; and 4-bromo-3′-nitrodiphenyl, 774 cm.$^{-1}$. These measurements enabled the composition of mixtures of isomers to be calculated by the method described by Augood, Hey, and Williams,[15] the amounts of 4-chloro-4′-nitrodiphenyl and 4-bromo-4′-nitrodiphenyl being obtained by difference. The accuracy of the determinations was tested by the preparation and analysis of synthetic mixtures of known composition of the two sets of isomers. The results obtained are given in Table 2.

TABLE 2. *Analyses of mixtures of known composition.*

| | | | Composition of $p$-X·$C_6H_4$·$C_6H_4$·$NO_2$ | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Known (%) | | | Found (%) | | |
| Mixture | Method | X in $p$-X·$C_6H_4$·$C_6H_4$·$NO_2$ | 4 : 2′- | 4 : 3′- | 4 : 4′- | 4 : 2′- | 4 : 3′- | 4 : 4′- |
| $S_1$ | Infrared | Cl | 45·8 | 24·9 | 29·3 | 43·2 | 26·0 | 30·8 |
| $S_2$ | ,, | Br | 59·5 | 30·0 | 10·5 | 59·4 | 29·7 | 10·9 |
| $S_3$ | ,, | Br | 59·1 | 29·7 | 11·2 | 59·9 | 30·5 | 9·6 |
| $S_4$ | Isotope diln. | Br | 29·3 | 9·8 | 60·9 | 29·5 | 10·3 | 60·2 |

The reliability of the method of analysis is demonstrated by these results. The analyses of the products of *p*-chlorophenylation and *p*-bromophenylation of nitrobenzene (experiments 1—6) are given in Table 3.

*Analysis of Mixtures of Isomers by the Ultraviolet Method.*—The determination of the ratios of isomers present in the mixture of isomeric nitrodiphenyls formed in experiments 7 and 8 was carried out by ultraviolet spectrophotometry with the aid of a Unicam " S.P. 500 " quartz spectrophotometer, the method of calculation described by Cadogan, Hey, and Williams [16] being used. The calibration curves for the pure isomers were those obtained by Hey, Stirling, and Williams.[6] Spectra were taken by reading the extinction coefficient at intervals of 2 mμ in the range 230—320 mμ. Measurements on the spectra were made at six pairs of wavelengths, and the ratio of isomers calculated from each pair. The results are given in Table 4. The accuracy of the determinations was checked by using the mean composition of the mixture, as

[15] Augood, Hey, and Williams, *J.*, 1953, 44.
[16] Cadogan, Hey, and Williams, *J.*, 1954, 794.

determined, in conjunction with the known calibration spectra of the pure isomers to calculate the extinction coefficient of the mixture at each wavelength at which this had been measured. Comparison of these values with the observed extinction coefficients showed completely satisfactory accuracy; the standard deviation from the mean error (−0·75%) for the determination of the composition of the mixture of nitrodiphenyls was ±1·24%. The method of analysis was therefore considered satisfactory.

TABLE 3. *Analysis of products of* p-*halogenophenylation of nitrobenzene.*

| Exp. no. | Method | X in *p*-X·C$_6$H$_4$·C$_6$H$_4$·NO$_2$ | Composition of *p*-X·C$_6$H$_4$·C$_6$H$_4$·NO$_2$ (%) 4 : 2′- | 4 : 3′- | 4 : 4′- |
|---|---|---|---|---|---|
| 1 | Infrared | Cl | 58·3 | 14·0 | 27·7 |
| 2 | ,, | Cl | 59·6 | 13·5 | 26·9 |
| Mean | ,, | Cl | 59·0 | 13·8 | 27·2 |
| 3 | ,, | Br | 57·9 | 13·6 | 28·5 |
| 4 | ,, | Br | 59·7 | 13·3 | 27·0 |
| Mean | ,, | Br | 58·8 | 13·5 | 27·7 |
| 5 | Isotope diln. | Br | 57·1 | 12·9 | 30·0 |
| 6 | ,, | Br | 56·2 | 12·8 | 31·0 |
| Mean | ,, | Br | 56·6 | 12·9 | 30·5 |

TABLE 4. *Analysis of products obtained in the phenylation of nitrobenzene.*

| Wavelength pair | Composition (%) 2- | 3- | 4- | Wavelength pair | Composition (%) 2- | 3- | 4- |
|---|---|---|---|---|---|---|---|
| | Experiment 7 | | | | Experiment 8 | | |
| 258, 306 | 61·7 | 10·7 | 27·6 | 258, 306 | 62·2 | 10·0 | 27·8 |
| 266, 300 | 61·9 | 10·6 | 27·5 | 266, 300 | 62·8 | 9·9 | 27·3 |
| 254, 310 | 62·0 | 10·3 | 27·7 | 254, 310 | 62·7 | 9·8 | 27·5 |
| 250, 294 | 62·6 | 9·1 | 28·3 | 250, 294 | 64·9 | 8·0 | 27·1 |
| 262, 302 | 61·8 | 10·5 | 27·7 | 262, 302 | 62·5 | 10·2 | 27·3 |
| 246, 290 | 61·5 | 10·1 | 28·4 | 246, 290 | 63·4 | 8·8 | 27·8 |
| | | | | Mean (expts. 7 & 8) | 62·5 | 9·8 | 27·7 |

*Analysis of Mixtures of Isomers by the Isotope-dilution Method.*—The mixtures of isomeric 4-bromonitrodiphenyls from experiments 5 and 6 were analysed by the isotope-dilution method. Mixtures of inactive materials were first used in order to develop a method of isolation of pure samples of at least two of the isomers. It was possible to isolate 4-bromo-2′- and -4′-nitrodiphenyl by fractional crystallisation. The following procedure was therefore adopted for the analysis. Two portions (0·4—0·8 g.) of the mixture of isomers obtained from each of experiments 5 and 6 were diluted, one with labelled 4-bromo-4′-nitrodiphenyl (10—25 mg.; portion A) and the other with labelled 4-bromo-2′-nitrodiphenyl (10—25 mg.; portion B). Mixture A was dissolved in hot ethanol and crystallised. The 4-bromo-4′-nitrodiphenyl which separated was purified by crystallisation 9 times from ethanol, and its specific activity measured. The m. p. (176°) and specific activity were checked before and after the last crystallisation: the difference was negligible. Portion B was dissolved in hot ethanol and the solution cooled. The 4-bromo-4′-nitrodiphenyl which separated was discarded. On evaporation and cooling of the mother-liquor, 4-bromo-2′-nitrodiphenyl was obtained, which was purified by recrystallisation (11 times) from light petroleum to constant m. p. (65°) and specific activity.

In this way the mixtures were analysed for 4-bromo-2′- and 4′-nitrodiphenyl, the proportion of the third isomer, 4-bromo-3′-nitrodiphenyl, being obtained by difference. In order to check the accuracy of the determinations, a synthetic mixture of known composition was analysed, with the results given in Table 2.

The results obtained for the analysis of the experimental mixtures are given in Table 3.

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## 384. *Amino-sugars and Related Compounds. Part III.* Acid Reversion of 2-Acetamido-2-deoxy-D-glucose (N-Acetyl-D-glucosamine).*

By A. B. Foster and D. Horton.

Prolonged exposure of 2-acetamido-2-deoxy-D-glucose to moist hydrogen chloride vapour causes the formation of a series of oligosaccharides (reversion). Two disaccharides have been isolated from the mixture. Evidence is presented which indicates their structures to be 2-acetamido-6-*O*-(2-acetamido-2-deoxy-α- and -β-D-glucopyranosyl)-2-deoxy-D-glucose.

The polymerisation (reversion) of D-glucose under certain acidic conditions to yield oligosaccharides has been well studied. Reversion may occur in acidic aqueous solutions [1] or on prolonged exposure to moist hydrogen chloride vapour.[2] The latter method has been adopted in these investigations; it has also been successfully applied to D-xylose [3] and L-rhamnose.[4]

In preliminary experiments it was observed that 2-amino-2-deoxy-D-glucose hydrochloride was unaffected by prolonged exposure to moist hydrogen chloride vapour. This is probably due to the positive charge acquired by the amino-group in acid media which electrostatically shields the glycosidic centre and prevents the approach of hydrions. Thus, under normal reaction conditions, 2-amino-2-deoxy-D-glucose hydrochloride resists glycosidation when treated with methanolic hydrogen chloride [5] and methyl 2-amino-2-deoxy-D-glucopyranoside is hydrolysed very slowly by aqueous acid.[5] The whole amino-sugar molecule appears to be electrostatically shielded by the $^{-}NH_3^{+}$ group, since 2-amino-2-deoxy-D-glucose hydrochloride is not incorporated into the oligosaccharides produced when a mixture of D-galactose and the amino-sugar derivative is exposed to moist hydrogen chloride vapour.[4]

Exposure of 2-acetamido-2-deoxy-D-glucose (*N*-acetyl-D-glucosamine) to moist hydrogen chloride vapour for four weeks gave a series of oligosaccharides from which two of the lower members *A* and *B* were separated and purified by chromatography on charcoal–Celite. Evidence is presented which indicates that *A* is 2-acetamido-6-*O*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-2-deoxy-D-glucose and that *B* is 2-acetamido-6-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucose.

The behaviour of *A* and *B* in charcoal–Celite and paper chromatography was similar to that of di-*N*-acetylchitobiose [6] and indicated them to be disaccharides; this was substantiated by elemental analysis and proved by hypoiodite oxidation. Both *A* and *B* were isolated crystalline and both exhibited slight downward mutarotation on dissolution in water.

*A* and *B* responded to the Morgan–Elson test [7] for *N*-acylamino-sugars and gave colours with intensities equivalent to 127% and 136% respectively of that given by an equimolar quantity of 2-acetamido-2-deoxy-D-glucose. These observations indicate that the glycosidic linkage in both *A* and *B* is 1 ⟶ 6 since Jeanloz and Trémège [8] have found that whereas 2-acetamido-2-deoxy-6-*O*-methyl-D-glucose yields a colour equivalent to 160% of that given by an equimolar amount of 2-acetamido-2-deoxy-D-glucose, the 3-*O*- and 4-*O*-methyl derivatives produce respectively 100% and 3% of the colour. Related results have been obtained by Kuhn, Baer, and Gauhe [9] with certain disaccharides.

* Part II, *J.*, 1957, 81.

[1] Thompson, Anno, Wolfrom, and Inatome, *J. Amer. Chem. Soc.*, 1954, **76**, 1309.
[2] Ricketts, *J.*, 1954, 4031.
[3] Bishop, *Canad. J. Chem.*, 1956, **34**, 1255.
[4] Foster and Horton, unpublished results.
[5] Moggridge and Neuberger, *J.*, 1938, 745; cf. Foster and Stacey, *Adv. Carbohydrate Chem.*, 1952, **7**, 247.
[6] Barker, Foster, Stacey, and Webber, *Chem. and Ind.*, 1957, 208.
[7] Morgan and Elson, *Biochem. J.*, 1934, **28**, 988.
[8] Jeanloz and Trémège, *Fed. Proc.*, 1956, **15**, 282.
[9] Kuhn, Baer, and Gauhe, *Chem. Ber.*, 1954, **87**, 1138, 1553.

Caution must be exercised in the interpretation of the reaction of *N*-acetylated amino-sugar derivatives with periodate since an adequate explanation of the reaction of 2-acetamido-2-deoxy-D-glucose itself is lacking. However it may reasonably be inferred that, since *A* consumes 5·95 mols. of oxidant, yielding 3·6 mols. formic acid but no formaldehyde, the non-reducing moiety is not a furanoside and the glycosidic linkage is possibly 1⟶6.

More reliable information on the position of the glycosidic linkage in *A* and *B* was obtained by periodate oxidation of their reduced derivatives. With sodium borohydride *A* and *B* readily yielded 2-acetamido-6-*O*-(2-acetamido-2-deoxy-α- and -β-D-glucopyranosyl)-2-deoxy-D-glucitol, (*A'*) and (*B'*) respectively. Both *A'* and *B'* rapidly (5 min.) consumed approximately 2 mols. of periodate with the concomitant release of approximately 1 mol. of formic acid, and slowly ($t_{\frac{1}{2}}$, 3—4 hr.) consumed a further mol. of oxidant. Formaldehyde was not liberated in the oxidation of *A'* and to an insignificant extent (<0·02 mol.) in the case of *B'*. These results, which are consistent with the structures allocated to *A'* and *B'*, indicate a rapid reaction of the acyclic moieties with periodate and a slow cleavage of the pyranoside moieties. This difference in reactivity would be expected from the behaviour of the model compounds 2-acetamido-2-deoxy-D-glucitol, which consumed 3 mols. of periodate within 5 min. with the concomitant release of formic acid (2 mols.) and formaldehyde (1 mol.), and methyl 2-acetamido-2-deoxy-α-D-glucopyranoside which slowly ($t_{\frac{1}{2}}$ *ca.* 2 hr.) consumed 1 mol. of oxidant. Over-oxidation was not observed with the non-reducing amino-sugar derivatives. Reduction of the product, presumably α-acetamido-α-deoxy-L-glyceraldehyde, obtained by periodate oxidation of 2-acetamido-2-deoxy-D-glucitol, gave 2-acetamidopropane-1 : 3-diol; acidic hydrolysis of this compound gave the amino-diol hydrochloride.

TABLE 1. *Optical rotation data for A', B', and related compounds.*

| Compound | $[M]_D$ [a] | Compound | $[M]_D$ [a] | 2A [b] | 2B [b] |
|---|---|---|---|---|---|
| *A'* | +328° | *B'* | −94° | 422 | 234 |
| Me 2-acetamido-2-deoxy-α-D-gluco-pyranoside [10] | +308 | Me 2-acetamido-2-deoxy-β-D-gluco-pyranoside [11] | −104 | 412 | 204 |
| Isomaltitol [12] | +306 | Gentiobiitol [13] | −82 | 388 | 224 |

[a] Rotations determined in water. [b] Calc. by Hudson's method.[14] 2A = contribution of $C_{(1)}$; 2B = contribution of remainder of molecule.

Attempts to prove the molecular weight of compound *A* by determination of the 2-amino-2-deoxy-D-glucose liberated on acidic hydrolysis of the reduced derivative *A'* were unsuccessful. Under normal conditions of acidic hydrolysis (2N-acid at 100° for 3—4 hr.), 32% release of the amino-sugar was observed (calc. 51%), which did not significantly increase on prolonged hydrolysis, probably because hydrolysis yielded, in addition to 2-amino-2-deoxy-D-glucose, an acid-resistant product (presumably de-*N*-acetylated *A'*). This phenomenon has been described in detail in Part II.

Evidence which indicates the configuration of the linkages in *A* and *B* to be respectively α and β was obtained from several sources.

The optical rotation data in Table 1 illustrate the relation of *A'* and *B'* to the anomeric methyl 2-acetamido-2-deoxy-D-glucopyranosides and to the D-glucose derivatives isomaltitol and gentiobiitol. Application of Hudson's isorotation rules to *A'* and *B'* gave 2A and 2B values closely similar to those obtained for the related compounds in Table 1, again emphasising the structural relation.

The frequencies (cm.$^{-1}$) of the infrared absorption in the range 750—1000 cm.$^{-1}$ for *A*, *B*, and related compounds are shown in Table 2. The type 2a absorption at *ca.* 840 cm.$^{-1}$

[10] Kuhn, Zilliken, and Gauhe, *Chem. Ber.*, 1953, **86**, 466.
[11] Kuhn and Baer, *ibid.*, p. 724.
[12] Wolfrom, Thompson, O'Neill, and Galkowski, *J. Amer. Chem. Soc.*, 1952, **74**, 1062.
[13] Wolfrom and Gardner, *ibid.*, 1943, **65**, 750.
[14] Hudson, *ibid.*, 1909, **31**, 66.

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which is indicative [15] of α-glucopyranosides is shown by methyl 2-acetamido-2-deoxy-α-D-glucopyranoside, *A*, and *A'*, but not by the corresponding isomeric compounds methyl 2-acetamido-2-deoxy-β-D-glucopyranoside, *B*, and *B'*. Since *A'* contains only one glycosidic centre the absorption at 843 cm.$^{-1}$ substantiates the allocation of an α-linkage to both *A* and *A'*. No inference can be drawn from the absorption of *B'* at 900 cm.$^{-1}$; although it falls near to the range (891 ± 7 cm.$^{-1}$) of the type 2b absorption indicative [15] of β-glucopyranosidic linkages, 2-acetamido-2-deoxy-D-glucitol absorbs in this range (892 cm.$^{-1}$). The absence of absorption at *ca.* 840 cm.$^{-1}$ in *B'* may be taken as negative evidence for the presence of a β-linkage.

It has been observed [16] that whilst glycosidic derivatives of 2-acetamido-2-deoxy-α-D-glucopyranose are ineffective as growth factors for *Lactobacillus bifidus* var. *Penn.*, the β-anomers are frequently active. Consistently with these observations, *A* was found [17] to be completely inactive; apparently the organism is unable to hydrolyse the disaccharide since 2-acetamido-2-deoxy-D-glucose has weak growth-factor activity. On the other

TABLE 2. *Frequencies (cm.$^{-1}$) of infrared absorptions (750—1000 cm.$^{-1}$) of* A, B, *and related compounds.*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Me 2-acetamido-2-deoxy-α-D-glucopyranoside [a] | 951s | 925w | 896s | 857w | 840m | 778w | 765w, 758m |
| Me 2-acetamido-2-deoxy-β-D-glucopyranoside [a] | — | 935m | 896m, 860m | — | — | — | — |
| *A* | 973s | — | 919m | 861w | 844m, 836w | 776s | — |
| *B* | 961m | 945m | 892w | 860vw | — | 778w | — |
| *A'* | 964m | 924m | 892m | 860sh | 834m | 775sh | 750sh |
| *B'* | 955m | — | 900m | — | — | — | — |
| 2-Acetamido-2-deoxy-D-glucitol | 966m | 939m | 892m | 876s | — | — | 761w |

[a] Data taken from ref. 15. w = weak; m = medium; s = strong; v = very; sh = shoulder.

hand, *B* showed activity at quite a high level (200 μg./unit). For comparison one of the most active growth factors so far discovered for *L. bifidus* var. *Penn.*, 2-acetamido-2-deoxy-4-*O*-(β-D-galactopyranosyl)-D-glucose,[16] has an activity of 80 μg./unit.

The evidence presented above indicates that the predominant disaccharides formed in the acid reversion of 2-acetamido-2-deoxy-D-glucose are linked α1⟶6 and β1⟶6. In their work on the acid reversion of D-glucose, using the aqueous acid method, Wolfrom *et al.*[1] found that isomaltose (α1⟶6 link) and gentiobiose (β1⟶6 link) were formed in approximately equal amounts but far in excess of any other disaccharide. Ricketts and Rowe [18] observed that the polymer produced on reversion of D-glucose contained predominantly 1⟶6 links.

## EXPERIMENTAL

Unless otherwise stated, chromatography was performed on Whatman No. 1 paper by irrigation with the organic phase of a butanol–ethanol–water–ammonia (40 : 10 : 49 : 1) solvent system; $R_F$ values refer to this system. Reducing sugars were detected with aniline hydrogen phthalate,[19] non-reducing carbohydrates with the silver nitrate–sodium hydroxide reagent,[20] and compounds containing free amino-groups with ninhydrin.

*Acid Reversion of 2-Acetamido-2-deoxy-D-glucose.*—2-Acetamido-2-deoxy-D-glucose (10 g.) was exposed to moist hydrogen chloride [2] for 4 weeks. Paper chromatography of the product revealed a series of reducing oligosaccharides (of which the lower members *A*, *B*, *C*, and *D* had $R_F$ values 0·11, 0·08, 0·06, and 0·04 respectively), together with 2-amino-2-deoxy-D-glucose and its *N*-acetyl derivative. Negligible amounts of ninhydrin-positive material with $R_F$ value

[15] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.
[16] Zilliken, Smith, Rose, and György, *J. Biol. Chem.*, 1954, **208**, 299; 1955, **217**, 79.
[17] György, Norris, and Rose, *Arch. Biochem. Biophys.*, 1954, **48**, 193.
[18] Ricketts and Rowe, *J.*, 1955, 3809.
[19] Partridge, *Nature*, 1949, **164**, 443.
[20] Trevelyan, Procter, and Harrison, *ibid.*, 1950, **166**, 444.

less than that of 2-amino-2-deoxy-D-glucose was detected. The oligosaccharides produced on acidic hydrolysis of chitosan [6] react strongly with ninhydrin. *A* and *C* gave an identical characteristic reddish-brown colour with aniline hydrogen phthalate; *B* and *D* gave an identical grey-brown colour.

Fractionation of the saccharide mixture on a charcoal–Celite column [21] (5·5 × 30 cm.), using gradient elution [22] with aqueous ethanol (0 ⟶ 35% in 9 l.), led to the isolation of *A* (0·733 g.) and *B* (0·303 g.) which appeared homogeneous by paper chromatography. Fractions which contained 2-acetamido-2-deoxy-D-glucose, *A*, and *C* were strongly dextrorotatory, but those containing *B* and *D* had negligible optical activity. *B* emerged from the column before *A*, and *D* before *C*. In separate experiments it was shown that saccharides other than *A*, *B*, *C*, and *D*, and presumably of higher molecular weight, were present. None of these was isolated pure.

Crystallisation of *A* from ethanol occurred during 8 months and after recrystallisation from the same solvent 2-acetamido-6-*O*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-2-deoxy-D-glucose was obtained, having m. p. 215°, $[M]_D^{13}$ +593° (initial, by extrapolation) ⟶ +564° (45 min.) ⟶ +530° (equilibrium, 24 hr.) (*c* 1·0 in $H_2O$), $M_G$ value [23] 0·19 (borate buffer,[24] pH 10) (Found: C, 45·2; H, 6·5; N, 6·6. $C_{16}H_{28}O_{11}N_2$ requires C, 45·3; H, 6·6; N, 6·6%).

After crystallisation from ethanol–ether 2-acetamido-6-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucose (*B*) was obtained, with m. p. 200° (decomp.), $[M]_D^{15·5}$ +51° (initial, by extrapolation) ⟶ +43° (45 min.) ⟶ +27° (equilibrium, 24 hr.) (*c* 1·2 in $H_2O$), $M_G$ 0·18 (Found: C, 45·1; H, 6·9; N, 6·5%).

Both *A* and *B* were very hygroscopic and on acidic hydrolysis *A* gave 2-amino-2-deoxy-D-glucose (which was isolated as the crystalline hydrochloride), and a second product ($R_F$ 0·05), presumably the corresponding de-*N*-acetylated disaccharide (see Part II [25]).

*Hypoiodite Oxidation of* A *and* B.—Both *A* and *B* were oxidised by hypoiodite at 2° under essentially the conditions described by Jeanloz and Forchielli; [26] 2-acetamido-2-deoxy-D-glucose was used as control. Reaction was complete within 12 hr., although *B* was oxidised more slowly than was *A* or the control. On the assumption of one reducing group per saccharide molecule the following mol. wts. were obtained: *A*, 435; *B*, 420 (Calc. for $C_{16}H_{28}O_{11}N_2$: 424) [control, 221 (Calc. for $C_8H_{15}O_6N$: 221)].

*Behaviour of* A *and* B *in the Morgan–Elson* [7] *Test.*—Aliquot parts (1 ml.) of 0·01% aqueous solutions of *A* and *B* were introduced separately into special graduated tubes [27] and treated successively with sodium carbonate and *p*-dimethylaminobenzaldehyde according to the procedure of Aminoff, Morgan, and Watkins; [28] 2-acetamido-2-deoxy-D-glucose was used as control. The absorptions of the coloured derivatives were measured with a "Spekker" photoelectric absorptiometer (H760, Hilger and Watts Ltd.), in 1 cm. cells with Ilford No. 605 filters (maximal transmission at 550 mμ). *A* and *B* gave, respectively, colour intensities equivalent to 127% and 136% of that produced by an equimolar amount of the control. Under the same conditions 2-acetamido-4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucose (di-*N*-acetylchitobiose [6]) gave 3% of the colour produced by an equimolar amount of 2-acetamido-2-deoxy-D-glucose. The absorption spectra of the coloured derivatives formed from *A*, *B*, and 2-acetamido-2-deoxy-D-glucose were closely similar in form in the range 460—640 mμ.

*Reduction of* A *and* B.—A solution of *A* (282 mg.) in water (20 ml.) was treated with sodium borohydride (42·2 mg.) in water (5 ml.). After 3 hr. the solution was acidified with dilute acetic acid and de-ionised with Amberlite resins IR-120 ($H^+$) and IRA-400 ($HO^-$). Evaporation of the ion-free solution gave a syrup which crystallised from 90% ethanol, to give *2-acetamido-6-O-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-2-deoxy-D-glucitol hydrate* (*A'*) (136 mg., 48%), m. p. 116° (evolution of gas), $[M]_D$ +328° (*c* 0·1 in $H_2O$), $M_G$ 0·54 (borate buffer,[24] pH 10) (Found: C, 43·5; H, 7·3; N, 6·4. $C_{16}H_{30}O_{11}N_2,H_2O$ requires C, 43·2; H, 7·2; N, 6·3%). *A'* which was extremely hygroscopic could be dried to constant weight at 46° *in vacuo* over

[21] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.
[22] Lindberg and Wickberg, *Acta Chem. Scand.*, 1954, **8**, 569.
[23] Foster, *J.*, 1953, 982.
[24] Foster, Newton-Hearn, and Stacey, *J.*, 1956, 30.
[25] Foster, Horton, and Stacey, *J.*, 1957, 81.
[26] Jeanloz and Forchielli, *J. Biol. Chem.*, 1951, **188**, 361.
[27] Belcher, Nutten, and Sambrook, *Analyst*, 1954, **79**, 201.
[28] Aminoff, Morgan, and Watkins, *Biochem. J.*, 1952, **51**, 379.

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$P_2O_5$. Elevation of the temperature to 135° caused a 4·2% loss in weight (calc. loss 4·1% for a monohydrate).

Compound *B* (64·6 mg.) was reduced to give, after crystallisation from alcohol, 2-*acetamido*-6-O-(2-*acetamido* 2-*deoxy*-β-D-*glucopyranosyl*)-2-*deoxy*-D-*glucitol* (*B'*) (22·7 mg., 35%), m. p. 201—202°, $[M]_D$ −94° (*c* 2·1 in $H_2O$), $M_G$ 0·57 (Found: C, 45·2; H, 7·3; N, 6·2. $C_{16}H_{30}O_{11}N_2$ requires C, 45·1; H, 7·0; N, 6·6%).

*Acidic Hydrolysis of* 2-*Acetamido*-6-O-(2-*acetamido*-2-*deoxy*-α-D-*glucopyranosyl*)-2-*deoxy*-D-*glucitol* (A').—A solution of *A'* (1 mg.) in 2N-hydrochloric acid (1 ml.) was heated at 100°, then neutralised with N-sodium carbonate, and the volume made up to 10 ml. 2-Amino-2-deoxy-D-glucose was determined in aliquot parts (1 ml.) of this solution by the procedure given in detail in Part II.[25] Maximum release of amino-sugar was 32% (calc., 51%) which occurred within 4 hr., and did not significantly increase after a further 4 hr.

*Periodate Oxidations.*—(a) 2-*Acetamido*-6-O-(2-*acetamido*-2-*deoxy*-α-D-*glucopyranosyl*)-2-*deoxy*-D-*glucose* (A). A solution containing sodium metaperiodate (1·25 millimoles) and *A* (20 mg.) in water (50 ml.) was stored at room temperature in the dark. The consumption of periodate was followed in the usual way and found to be complete at 5·95 mols. (mean of 2 results) after 72 hr. After 88 hr., 3·6 mols. of formic acid had been formed, which rose to 3·87 after 167 hr. No formaldehyde was liberated (dimedone).

(b) 2-*Acetamido*-6-O-(2-*acetamido*-2-*deoxy*-α-D-*glucopyranosyl*)-2-*deoxy*-D-*glucitol* (A'). *A'* (30 mg.), when treated with periodate as in (a), consumed 1·95 mols. of oxidant within 5 min. and released 1·04 mols. of formic acid during 1 hr. After 24 hr. 3·01 mols. of oxidant had been consumed with no further increase in the formic acid production. Formaldehyde could not be detected (dimedone). No over-oxidation was observed after 24 hr.

Paper chromatography of the products revealed a component [$R_F$ 0·63; organic phase of butanol–water–acetic acid (4 : 5 : 1)] with behaviour identical with that of α-acetamido-α-deoxy-L-glyceraldehyde

(c) 2-*Acetamido*-6-*O*-(2-*acetamido*-2-*deoxy*-β-D-*glucopyranosyl*)-2-*deoxy*-D-*glucitol* (B'). *B'* (15·5 mg.), when treated with periodate as in (a), rapidly consumed 1·9 mols. of oxidant with the release of 0·81 mol. of formic acid. After 24 hr. 3·1 mols. of oxidant had been consumed, and 0·86 mol. of formic acid produced, with a trace of formaldehyde. In separate experiments the formaldehyde produced was <0·02 mol. as determined by the chromotropic acid method.[29]

(d) 2-*Acetamido*-2-*deoxy*-D-*glucitol*. A solution of 2-acetamido-2-deoxy-D-glucitol (2·1 g., 9·6 millimoles) was oxidised with 0·9N-periodic acid (56 ml., 50 millimoles) at room temperature for 15 min. After neutralisation with barium carbonate and centrifugation the supernatant liquid was hydrogenated in the presence of Raney nickel (W2) at 100°/75 atm. Catalyst was removed and the filtrate de-ionised with Amberlite resins IR-120 ($H^+$) and IRA-400 ($HO^-$). Evaporation of the solution and recrystallisation (twice) of the residue (1·08 g., 70%) from methanol–ethyl acetate gave 2-*acetamidopropane*-1 : 3-*diol*, m. p. 89—90° (Found: C, 45·1; H, 8·3; N, 10·7. $C_5H_{11}O_3N$ requires C, 45·1; H, 8·3; N, 10·5%).

In a parallel experiment, paper chromatography of the supernatant liquid before hydrogenation, with the organic phase of butanol–water–acetic acid (4 : 5 : 1), showed a single component ($R_F$ 0·63), presumably α-acetamido-α-deoxy-L-glyceraldehyde.

Hydrolysis of 2-acetamidopropane-1 : 3-diol (0·255 g.) in N-hydrochloric acid (30 ml.) at 100° for 2 hr., followed by evaporation of the solution and recrystallisation of the residue from ethanol–ethyl acetate, gave 2-*aminopropane*-1 : 3-*diol hydrochloride* (0·208 g., 87%), m. p. 104° (Found: N, 10·5; Cl, 27·8. $C_3H_{10}O_2NCl$ requires N, 11·0; Cl, 27·8%).

*Infrared Spectra.*—The spectra were determined by the KCl or KBr disc method.

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[29] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.

## 385. *Immunopolysaccharides. Part IX.* The Enzymic Synthesis of Trisaccharides containing the α-1 : 2-Glucosidic Linkage.*

By R. W. Bailey, S. A. Barker, E. J. Bourne, P. M. Grant, and M. Stacey.

A trisaccharide produced during the growth of *B. arabinosaceous* on a cellobiose–sucrose medium has been characterised as *O*-β-D-glucopyranosyl-(1 → 4)-*O*-[α-D-glucopyranosyl-(1 → 2)]-D-glucose. A similar trisaccharide elaborated in a lactose–sucrose medium has been characterised as *O*-β-D-galactopyranosyl-(1 → 4)-*O*-[α-D-glucopyranosyl-(1 → 2)]-D-glucose.

In previous papers in this series [1,2] it has been shown that the primary function of the dextransucrase of *Betacoccus arabinosaceous* (Birmingham) is the transfer of a glucosyl moiety from its specific substrate sucrose to some suitable receptor (isomaltose, D-glucose, methyl α-D-glucoside, 3-*O*-methyl-D-glucose, or a growing dextran chain) to which it becomes attached by an α-1 : 6-glucosidic linkage. It was envisaged that under certain conditions the presence of an unsuitable non-reducing moiety (*e.g.*, β-D-glucosyl or β-D-galactosyl) in a receptor disaccharide might tend to favour the attachment of the enzymically transferred glucose residue to the reducing moiety of the disaccharide, if this has an appropriate structure. Such a transfer has indeed been found to occur (for preliminary reports see Bailey, Barker, Bourne, and Stacey; [3] Barker, Bourne, Grant, and Stacey [4]) where the receptor disaccharides were cellobiose and lactose. We now report fully the structural characterisation of the two trisaccharides thus formed.

Chromatographically pure trisaccharide A (in a yield corresponding to 11% of the glucose available from the sucrose) was isolated from a sucrose–cellobiose culture medium by fractionation on a charcoal–Celite column.[5,6] When separated as its *N*-benzylglycosylammonium ion, compound A had the mobility expected [7] of a trisaccharide. Its molecular size was confirmed by oxidation with alkaline hypoiodite.[8] On total acidic hydrolysis only glucose (98% conversion) was detectable by paper chromatography or ionophoresis. Partial hydrolysis yielded glucose, cellobiose, and a disaccharide X.

The reducing power of trisaccharide A with the Shaffer–Hartmann copper reagent [9] was only 7·7% of the theoretical value for a trisaccharide. This discrepancy is shown generally by 2-*O*-substituted glucoses.[3,8] The compound was not disclosed by alkaline triphenyltetrazolium chloride which detects all reducing glucosaccharides except those with a 2-*O*-substituent.[10] Further evidence that the reducing unit was linked through position 2 was obtained when treatment with phenylhydrazine gave a mixture of cellobiosazone and glucosazone. The low mobility ($M_G$ 0·21) of the compound A on ionophoresis in borate buffer [11] was also indicative of a 1 : 2-linkage at the reducing group of the molecule.

Comparison of the specific rotation (+93°) of trisaccharide A with those of cellobiose (+35°) and maltotriose (+160°) suggested that one of the glycosidic linkages in the trisaccharide was α and the other β. Other evidence which confirmed this was (*a*) the

* Part VIII, *J.*, 1958, 601.

[1] Bailey, Barker, Bourne, and Stacey, *J.*, 1957, 3530.
[2] Barker, Bourne, Grant, and Stacey, *J.*, 1957, 3536.
[3] Bailey, Barker, Bourne, and Stacey, *Nature*, 1955, **176**, 1164.
[4] Barker, Bourne, Grant, and Stacey, *ibid.*, 1956, **178**, 1221.
[5] Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677.
[6] Lindberg and Wickberg, *Acta Chem. Scand.*, 1954, **8**, 569.
[7] Barker, Bourne, Grant, and Stacey, *J.*, 1957, 2067.
[8] Hirst, Hough, and Jones, *J.*, 1949, 928.
[9] Shaffer and Hartmann, *J. Biol. Chem.*, 1921, **45**, 377.
[10] Feingold, Avigad, and Hestrin, *Biochem. J.*, 1956, **64**, 351.
[11] Foster, *J.*, 1953, 982.

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presence of a peak at 840 cm.$^{-1}$ (α-linkage [12]) in the infrared spectrum (see Table) in addition to the peak at 894 cm.$^{-1}$ (β-linkage [12]) also shown by cellobiose, and (*b*) the action of almond β-glycosidase which produced glucose and disaccharide X. Disaccharide X, produced in this way, was shown to contain an α-glycosidic linkage by (*a*) its high specific rotation (+133°) and (*b*) the presence of a peak at 840 cm.$^{-1}$ in its infrared spectrum.

Disaccharide X was further characterised as 2-*O*-α-D-glucopyranosyl-D-glucose by (i) its low mobility on ionophoresis in borate buffer, (ii) its hydrolysis to glucose only (96% conversion), (iii) its low reducing power (27·5% of that calculated for a disaccharide) with Shaffer–Hartmann reagent,[9] (iv) its failure to react with alkaline triphenyltetrazolium chloride,[10] and (v) its stoicheiometric reaction with alkaline hypoiodite.[8] It was identical in its behaviour on paper chromatography and paper ionophoresis with a specimen of 2-*O*-α-D-glucopyranosyl-D-glucose synthesised chemically by Haq and Whelan.[13]

*Infrared spectra (cm.$^{-1}$) of trisaccharides A and B, together with those of reference oligosaccharides.*

| | | | | | | |
|---|---|---|---|---|---|---|
| Trisaccharide A | 914 | 894 | — | — | 840 | 780 |
| Cellobiose | 914 | 892 | — | — | — | 778 |
| Disaccharide X | 913 | — | — | — | 840 | 780 |
| Trisaccharide B | 914 | 889 | 872 | 851 | 844 | 780 |
| Lactose | 913 | 896 | 872 | — | — | 780 |
| Disaccharide Y | 913 | — | — | — | 840 | 780 |
| 2-*O*-α-D-Glucosyl-D-glucose | 913 | — | — | — | 840 | 780 |

From the evidence presented so far there are two possible structures for trisaccharide A, namely, (I) the "linear" *O*-β-D-glucopyranosyl-(1 → 4)-*O*-α-D-glucopyranosyl-(1 → 2)-D-glucose and (II) the "branched" *O*-β-D-glucopyranosyl-(1 → 4)-*O*-[α-D-glucopyranosyl-(1 → 2)]-D-glucose. From its mode of synthesis and the results of periodate oxidation of trisaccharide A [3·9 mols. of periodate consumed and 1·75 mols. of formic acid produced, leaving a fragment containing a glucose unit: theoretical values for (II) 4 mols. of periodate consumed and 2 mols. of formic acid produced] the structure of trisaccharide A was probably (II). This was confirmed by the results of periodate oxidation of the alcohol prepared from trisaccharide A by reduction with sodium borohydride. Trisaccharide A alcohol consumed 5·02 mols. of periodate and produced 1·92 mols. of formic acid and 0·85 mol. of formaldehyde, together with a product containing a xylose unit. [Theoretical for alcohols derived from (I) 6, 3, 1, and from (II) 5, 2, 1 respectively.] In addition, the alcohol consumed 5·2 mols. of lead tetra-acetate; only one of these was taken up rapidly, in conformity with structure (II), but not with (I).

Acidic hydrolysis of trisaccharide A alcohol resulted in 61·3% conversion into glucose; the other product of the hydrolysis was glucitol. On partial hydrolysis the products were glucose, glucitol, cellobiitol, and the alcohol derived from disaccharide X. The fact that two disaccharide alcohols were detected is further evidence in favour of structure (II).

Conclusive in favour of structure (II) were the products of hydrolysis of methylated trisaccharide A. One of the two methyl sugars appearing on a chromatogram was shown to be 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose by crystallisation of the free sugar and its anilide. The other was a di-*O*-methylhexose identical in its paper-chromatographic and -ionophoretic behaviour and in its infrared spectrum with 3 : 6-di-*O*-methyl-D-glucose.

Trisaccharide B was isolated, from a culture of *Betacoccus arabinosaceous* grown on a lactose–sucrose medium, in a yield corresponding to 31% of the glucose available from the sucrose. The structure of the trisaccharide was determined in a similar manner to that for trisaccharide A.

Compound B was shown to be a trisaccharide by the mobility of its *N*-benzylglycosylammonium ion [7] and by its almost stoicheiometric (96%) oxidation by alkaline hypoiodite.[8]

[12] Barker, Bourne, Stacey, and Whiffen, *J.*, 1954, 171.
[13] Haq and Whelan, *Nature*, 1956, **178**, 1221.

On total acidic hydrolysis, both glucose and galactose were produced (ratio approx. 2 : 1). Partial hydrolysis gave glucose, galactose, lactose, an unknown disaccharide Y, and residual trisaccharide B.

The reducing power with the Shaffer–Hartmann copper reagent [9] was only *ca.* 6·8% of the theoretical value for a trisaccharide. Trisaccharide B did not react with alkaline triphenyltetrazolium chloride [10] and on treatment with phenylhydrazine gave a mixture of lactosazone and glucosazone. These properties together with the low mobility in borate buffer [11] were all indications that the reducing unit of trisaccharide B was linked through position 2.

As with trisaccharide A there was ample evidence that one of the glycosidic linkages in trisaccharide B was α and the other β. Trisaccharide B had a high specific rotation (+103°) compared with that of lactose (+52°), showed a peak at both 889 cm.$^{-1}$ (β-linkage) and 844 cm.$^{-1}$ (α-linkage) and was converted by almond β-glycosidase into galactose and disaccharide Y. Disaccharide Y showed properties identical with those of disaccharide X and 2-*O*-α-D-glucopyranosyl-D-glucose in all respects. Additional experiments carried out with disaccharide Y were (i) its treatment with phenylhydrazine to yield D-glucosazone and (ii) periodate oxidation of its alcohol (4·9 mols. of periodate consumed, 2·8 mols. of formic acid and 0·9 mol. of formaldehyde produced; theor. for a 1 : 2-linked disaccharide alcohol are 5, 3, 1 respectively). With both disaccharide X and disaccharide Y, periodate oxidation of the free sugar resulted in over-oxidation, perhaps due to a malondialdehyde structure's being produced during oxidation.

Partial hydrolysis of the alcohol derived from trisaccharide B yielded two disaccharide alcohols; this indicated a "branched" structure similar to that of trisaccharide A. Trisaccharide B consumed 3·9 mols. of periodate with the production of 1·75 mols. of formic acid but no formaldehyde (theor. for a "branched" structure are 4, 2, and 0 respectively). Trisaccharide B alcohol consumed 4·9 mols. of periodate with the production of 1·91 mols. of formic acid and 0·85 mol. of formaldehyde (theor. 5, 2, and 1 respectively). Hydrolysis of the periodate-oxidised trisaccharide and its alcohol yielded components corresponding to glucose and xylose, respectively. Thus it was apparent that $C_{(2)}$ and $C_{(4)}$ of the reducing glucose unit were engaged in glycosidic linkages. This was supported by the initial rapid uptake of 1 mol. of lead tetra-acetate by trisaccharide B alcohol.

Conclusive for the structure *O*-β-D-galactopyranosyl-(1 ⟶ 4)-*O*-[α-D-glucopyranosyl-(1 ⟶ 2)]-D-glucopyranose were the products of hydrolysis of methylated trisaccharide B. Three spots were found on a chromatogram, characterised as those of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose, 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose, and 3 : 6-di-*O*-D-glucose.

The formation of branched trisaccharides by *B. arabinosaceous* is interesting as it involves the use of a carbohydrate primer in which a sugar residue, other than the usual non-reducing end unit, has the correct structure to act as an acceptor of a transferred sugar residue. This may be a general method for the formation of branched oligosaccharides and a possible route to the synthesis of branched polysaccharides which does not involve branching of a linear polymer as is the case with glycogen and amylopectin. It is interesting that the syntheses of trisaccharides A and B by the growing organism are accomplished by the formation in each case of an α-1 : 2-linkage and not the α-1 : 6-linkage usually produced by dextransucrase. Similar conversions have been effected by dextransucrase preparations, but the possibility that they are due to a second enzyme cannot be excluded. If, however, dextransucrase is responsible then it appears to be diverted from its preferred course of synthesis by the glycosidic substituent at position 4 of the receptor unit. This possibility will be examined further.

Cleavage of the β-linkages in trisaccharides A and B by almond β-glycosidase was extremely slow and in each case some 50% of the trisaccharide remained after 3 weeks. On the other hand the β-linkages of the two alcohols derived from the trisaccharides were completely hydrolysed in three days under comparable conditions. The reason for this marked difference undoubtedly lies in the fact that shielding of the β-linkage by the other

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non-reducing sugar ring would be far greater in each of the trisaccharides than in the alcohols, the central unit of which has a more flexible open-chain structure.

## Experimental

*Oligosaccharide Synthesis in a Cellobiose–Sucrose Medium.*—A sterile medium (100 ml.) was prepared containing yeast extract (1%), disodium ammonium phosphate (0·5%), potassium dihydrogen phosphate (0·1%), hydrated magnesium sulphate (0·05%) sucrose (10%), and cellobiose (30%). The medium was inoculated with *Betacoccus arabinosaceous* (Birmingham) and incubated at 25° for 3 days during which the pH fell from 7·0 to 4·1. Ethanol (100 ml.) was added, and the solution filtered and then adjusted to pH 7·0. The oligosaccharide mixture was fractionated [5,6] on a charcoal column (*l*, 60 cm.; diam. 8 cm.), the mono- and the disaccharide fractions were discarded, and a trisaccharide fraction A (1·56 g.) was obtained by elution with 12·5% aqueous ethanol (8 l.).

*Characterisation of Trisaccharide Fraction A.*—(i) Trisaccharide A had $[\alpha]_D^{18}$ +93° (equil.; *c* 1·00 in $H_2O$) and gave <0·5% of ash. Paper chromatography of the free sugar and of its benzylamine derivative [14] in the organic phase of butanol–ethanol–water–ammonia (40 : 10 : 49 : 1) showed that each moved as a single component with $R_{glucose}$ 0·14 and 0·32, respectively. The free sugar was detectable by aniline hydrogen phthalate [15] but not by alkaline triphenyltetrazolium chloride.[10] Paper ionophoresis [11] in borate buffer of pH 10 showed a single component ($M_G$ 0·21). When separated as its *N*-benzylglycosylammonium ion [7] in an electrolyte of sodium hydroxide–formic acid (pH 1·8) the mobility (*M*) was 0·54.

(ii) *Oxidation by hypoiodite and copper reducing value.* Under conditions in which glucose was oxidised stoicheiometrically by iodine in alkaline solution (Hirst, Hough, and Jones [8]), trisaccharide A (10 mg.) consumed iodine equivalent to 3·75 mg. of glucose (105% of the expected theoretical value for a trisaccharide).

When estimated by the Shaffer–Hartmann method,[9] trisaccharide A (20 mg. and 10 mg.) had a reducing power equivalent to 0·54 mg. and 0·28 mg. of glucose, respectively. This corresponded to 7·6 and 7·8%, respectively, of the calculated value for a trisaccharide.

(iii) *Hydrolysis.* Complete hydrolysis of trisaccharide A (1·95 mg.) in 1·5N-sulphuric acid (3 ml.) at 100° for 4 hr. gave glucose (identified on a paper chromatogram and ionophoretogram), equivalent to a 98% conversion. Paper chromatography of a partial hydrolysate (N-sulphuric acid for 1 hr. at 90°) of trisaccharide A showed components corresponding to glucose, cellobiose, trisaccharide A, and an unknown disaccharide X ($R_{glucose}$ 0·44). The presence of these components was confirmed by ionophoresis in borate buffer, pH 10; the disaccharide X had $M_G$ 0·32.

(iv) *Periodate oxidation.* Treatment of trisaccharide A (50·4 mg.) with 0·075M-sodium periodate (50 ml.) in the dark at room temperature gave the following results: The periodate consumption, expressed in moles per mole of trisaccharide A, was 1·0 (5 min.), 2·0 (10 min.), 2·7 (20 min.), 3·3 (60 min.), 3·9 (300 min.), 3·9 (1080 min.). After 1080 min., 1·75 moles of formic acid were produced per mole of trisaccharide A. No formaldehyde was produced.

Ethylene glycol (0·2 ml.) was added to part (10 ml.) of the fully oxidised solution. After removal of ions in a Consden desalting apparatus,[16] 4·5N-sulphuric acid (5 ml.) was added and the solution heated for 3 hr. at 100°. Paper-chromatographic and ionophoretic analysis of the neutralised hydrolysate indicated the presence of glucose.

(v) *Treatment with phenylhydrazine.* Trisaccharide A (0·10 g. in 1·7 ml.), when treated with phenylhydrazine (0·21 g.) and 50% acetic acid (0·21 ml.) at 100° for 2 hr., gave a mixture of osazones which was recrystallised twice from ethanol. Microscopical examination indicated the presence of cellobiosazone and glucosazone. The osazone mixture moved similarly to an authentic mixture of cellobiosazone and glucosazone when separated by paper ionophoresis in formate buffer of pH 1·8.

(vi) *Reduction of trisaccharide A.* Trisaccharide A (0·10 g.) in water (50 ml.) was reduced with sodium borohydride (0·11 g.) at room temperature for 2 hr. Amberlite IR-120 ($H^+$) (4 g.) was added, and the mixture shaken for 15 min., then filtered and evaporated to dryness *in*

[14] Bayly and Bourne, *Nature*, 1953, **171**, 385.
[15] Partridge, *Nature*, 1949, **164**, 443.
[16] Consden, Gordon, and Martin, *Biochem. J.*, 1947, **41**, 590.

*vacuo*. Dry methanol (3 × 25 ml.) was added and the whole evaporated to dryness *in vacuo*. The residue was dissolved in water and freeze-dried (73 mg.). The reduced trisaccharide A had $[\alpha]_D^{18}$ +89° (equil.; *c* 1·00 in $H_2O$) and moved as a single component ($R_{glucose}$ 0·19) in the solvent described above. It was not oxidised by alkaline hypoiodite [8] and had a negligible reducing power when determined by the Shaffer–Hartmann method.[9] The reducing sugars present in a complete hydrolysate (prepared as above) of trisaccharide A alcohol corresponded to 92% of the theoretical value. Paper chromatography of the hydrolysate and selective spraying with aniline hydrogen phthalate [15] and buffered bromocresol-purple revealed the presence of components having $R_F$ values identical with those of glucose and glucitol. Similar analysis of a partial hydrolysate (0·2N-sulphuric acid at 100° for 1 hr.) showed the presence of glucose, glucitol, cellobiitol, trisaccharide A alcohol, and the alcohol derived from disaccharide X.

Treatment of trisaccharide A alcohol (21·2 mg.) with sodium periodate as above gave the following results. The periodate consumption, expressed in moles per mole of trisaccharide A alcohol, was: 3·25 (15 min.), 4·48 (60 min.), 4·80 (120 min.), 4·92 (180 min.), 5·02 (1200 min.). After 1200 min., 1·92 moles of formic acid and 0·85 mole of formaldehyde were formed per mole of trisaccharide A alcohol. Desalting [16] and acidic hydrolysis of the fully oxidised reaction solution (as above) gave a component similar to a pentose on paper-chromatographic analysis and identical with L-xylose on paper-ionophoretic examination.

Treatment of trisaccharide A alcohol (10 mg.) with almond β-glycosidase (1·5 ml.) at 37° for 3 hr. gave a solution which, by paper chromatography, was found to contain glucose and disaccharide X alcohol. After 3 days, no trisaccharide A alcohol remained.

Treatment of trisaccharide A alcohol (8·5 mg.) in glacial acetic acid (23 ml.) with a saturated solution of lead tetra-acetate (2 ml.) consumed the following no. of moles per mole of trisaccharide A alcohol: 1·3 (15 min.), 1·3 (60 min.), 1·9 (180 min.), 3·2 (1080 min.), 5·2 (after 60 min. at 45°).

(vii) *Methylation*. Trisaccharide A (0·2 g.) was suspended in dioxan (20 ml.) and methylated with dimethyl sulphate (15 ml.) and 30% aqueous sodium hydroxide (30 ml.), added in ten equal portions at 10 min. intervals. The product was then methylated three times with the Purdie reagents. The resulting syrup (0·187 g.) was refluxed with 4% methanolic hydrogen chloride (30 ml.) for 6 hr., the solution neutralised with silver carbonate, and the filtrate concentrated to a syrup. This syrup was heated with 2N-hydrochloric acid (20 ml.) for 2 hr. at 100°, the solution again neutralised, and the filtrate concentrated to a syrup. Fractionation of the methyl sugars on a cellulose column with butanol–ethanol–water (40 : 10 : 50 v/v) gave fraction I (41 mg.) and fraction II (14 mg.).

Fraction I was identical with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose on paper chromatography and paper ionophoresis. On crystallisation, it had m. p. 90° undepressed on admixture with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose and showed $[\alpha]_D^{18}$ +83·5° (equil.; *c* 1·00 in $H_2O$). Treatment with aniline gave crystals, m. p. 136° alone or in admixture with *N*-phenyl-2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucosylamine.

Fraction II moved slightly more slowly than 2 : 3-di-*O*-methyl-D-glucose on a paper chromatogram and had $[\alpha]_D^{18}$ +60·3° (equil.; *c* 0·60 in $H_2O$) (Found: OMe, 27·1. Calc. for a di-*O*-methylhexose: OMe, 29·8%). Fraction II was identical with authentic 3 : 6-di-*O*-methyl-D-glucose both on paper chromatography and ionophoresis and in its infrared absorption spectrum.

(viii) *Treatment with almond emulsin*. Trisaccharide A (20 mg.) was added to almond β-glycosidase solution (3 ml. in 0·5M-acetate buffer of pH 5·0). Components identical with glucose (trace), disaccharide X (trace), and trisaccharide A were detected after incubation for 3 days. The hydrolysis continued, until after 3 weeks' incubation *ca.* 50% of trisaccharide A remained. Under similar conditions cellobiose was completely hydrolysed in 3 days.

*Characterisation of Disaccharide X*.—(i) *Isolation*. Trisaccharide A (0·20 g.) was treated with almond β-glycosidase solution (12 ml. as above) and incubated at 37° for 6 weeks. The products (glucose, disaccharide X, and trisaccharide A) were separated [5, 6] on a charcoal–Celite column (*l*, 40 cm.; diam., 2 cm.) by gradient elution with aqueous ethanol (0 ⟶ 12%). The first fraction (0·08 g.) eluted contained glucose, $[\alpha]_D^{20}$ +52° (equil.; *c* 1·00 in $H_2O$), characterised as D-glucosazone, m. p. and mixed m. p. 202°. The second fraction (0·024 g.), eluted with 5—6·5% aqueous ethanol contained disaccharide X, had $[\alpha]_D^{20}$ +133° (equil.; *c* 0·94 in $H_2O$), and gave <0·5% of ash. The third fraction (0·092 g.), eluted with 10—12% aqueous ethanol, contained trisaccharide A and had $[\alpha]_D^{20}$ +92° (equil.; *c* 1·00 in $H_2O$).

(ii) *Characterisation*. Disaccharide X could be detected on paper chromatograms by

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alkaline silver nitrate [17] and aniline hydrogen phthalate,[15] but not by alkaline triphenyltetrazolium chloride.[10] When oxidised by alkaline hypoiodite,[8] disaccharide X (3·4 mg.) consumed iodine equivalent to 1·76 mg. of glucose (98% of the theor. value for a disaccharide). When estimated by the cuprimetric Shaffer–Hartmann reagent,[9] disaccharide X (2·0 mg.) had a reducing power equivalent to 0·29 mg. of glucose (27·5% of the expected value for a disaccharide, a stoicheiometric reaction being assumed).

Complete hydrolysis of disaccharide X (as for trisaccharide A) gave glucose (identified on a paper chromatogram and ionophoretogram) equivalent to a 96% conversion. After oxidation of disaccharide X (4·2 mg.) with 0·075M-sodium periodate (10 ml.) for 15 hr., 6·1 moles of periodate were consumed and 2·85 moles of formic acid were produced per mole of disaccharide X. Disaccharide X alcohol (used above as a reference) was obtained by reduction of disaccharide X (4·0 mg.) with sodium borohydride (4·5 mg.) and isolated in a manner similar to that described above for trisaccharide A alcohol.

*Oligosaccharide Synthesis in a Sucrose–Lactose Medium.*—A sterile medium (250 ml.) was prepared containing yeast extract and salts as previously but with sucrose (2%) and lactose (10%), inoculated with *Betacoccus arabinosaceous* (Birmingham), and incubated at 25° for 3 days during which time the pH fell from 7·0 to 4·4. By a procedure similar to that used for trisaccharide A, a trisaccharide B (2·314 g.) was isolated from the culture fluid.

*Characterisation of Trisaccharide B.*—Unless otherwise stated the methods applied to trisaccharide B were the same as those for trisaccharide A.

(i) Trisaccharide B had $[\alpha]_D^{18}$ +103° (equil.; *c* 1·00 in $H_2O$) and gave <0·5% of ash. It moved as a single component when separated on a paper chromatogram (same solvent as above) either as the free sugar ($R_{glucose}$ 0·10) or as its benzylamine [14] derivative ($R_{glucose}$ 0·27). The free sugar was detectable by aniline hydrogen phthalate [15] but not by alkaline triphenyltetrazolium chloride.[10] On ionophoresis, the mobility of its borate complex was 0·33 and that of its *N*-benzylglycosylammonium ion [7] was 0·55.

(ii) *Oxidation by hypoiodite and copper reducing value.* With alkaline hypoiodite,[8] trisaccharide B (10 mg.) consumed iodine equivalent to 3·44 mg. of glucose (96% of the theor. value for a trisaccharide). When estimated by the Shaffer–Hartmann method,[9] trisaccharide B (20 mg. and 10 mg.) had a reducing power equivalent to 0·50 mg. and 0·24 mg. of glucose, respectively. This is 7·0% and 6·7% respectively of the calculated value for a trisaccharide.

(iii) *Hydrolysis.* Complete hydrolysis of trisaccharide B (1·86 mg.) gave a glucose–galactose mixture (identified on a paper chromatogram and ionophoretogram and estimated approx. as 2 : 1 ratio) which had a reducing power equivalent to 96% of the theoretical value. Paper chromatography of a partial hydrolysate of trisaccharide B showed components corresponding to glucose, galactose, lactose, trisaccharide B, and a disaccharide Y ($R_{glucose}$ 0·43). Ionophoresis in borate buffer (pH 10) showed components corresponding to glucose ($M_G$ 1·00), galactose ($M_G$ 0·93), lactose ($M_G$ 0·38), and trisaccharide B ($M_G$ 0·32). No separate spot was observed which could be attributed to disaccharide Y.

(iv) *Periodate oxidation.* Trisaccharide B (50·4 mg.), treated with sodium periodate as above, consumed 2·4 (5 min.), 3·05 (10 min.), 3·45 (20 min.), 3·6 (60 min.), 3·9 (300 min.), 3·9 (1080 min.) moles of periodate per mole. After 1080 min., 1·75 moles of formic acid were produced per mole. No formaldehyde was produced. Hydrolysis of the fully oxidised solution gave glucose.

(v) *Treatment with phenylhydrazine.* Osazones (0·37 g.) were formed from trisaccharide B (0·30 g.; method as above). After two recrystallisations from aqueous ethanol, the product (0·23 g.) was found to behave similarly to a mixture of lactosazone and glucosazone on ionophoresis in formate buffer (pH 1·8) and on circular paper chromatograms.

(vi) *Reduction of trisaccharide B.* Trisaccharide B (0·10 g.) was reduced with sodium borohydride to the alcohol (0·071 g.) which had $[\alpha]_D^{18}$ +99·5° (equil.; *c* 1·00 in $H_2O$) and moved as a single component ($R_{glucose}$ 0·16) in the solvent described above. It was not oxidised by alkaline hypoiodite [8] and had a negligible reducing power when determined by the Shaffer–Hartmann method.[9] Paper-chromatographic and -ionophoretic analyses of the complete hydrolysate of the alcohol indicated the presence of glucose, galactose, and glucitol. Similar analyses of the partial hydrolysate indicated the presence of glucose, galactose, glucitol, lactitol, disaccharide Y alcohol, and trisaccharide B alcohol.

[17] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.

Treatment of trisaccharide B alcohol (23·7 mg.) with sodium periodate resulted in the consumption of 3·65 (15 min.), 4·25 (60 min.), 4·58 (120 min.), 4·78 (180 min.), 4·90 (1200 min.) moles of periodate per mole. After 1200 min., 1·91 moles of formic acid and 0·85 mole of formaldehyde were produced per mole. Desalting and hydrolysis of the fully oxidised reaction solution yielded a component similar to a pentose on paper chromatography and identical with L-xylose on paper ionophoresis.

Incubation of trisaccharide B alcohol with almond β-glycosidase at 37° for 3 hr. gave a solution which, by paper chromatography, was found to contain galactose and disaccharide Y alcohol. Trisaccharide B alcohol was not detected in the digest after 72 hr.

Trisaccharide B alcohol (5·1 mg.) consumed 1·1 (15 min.), 1·1 (60 min.), 1·6 (180 min.), 2·7 (1080 min.), 4·9 (at 45° for 60 min.) moles of lead tetra-acetate per mole.

(vii) *Methylation.* Trisaccharide B (0·20 g.) was methylated as described above and the resulting syrup (0·17 g.) hydrolysed under the same conditions. Fractionation of the methyl sugars on a cellulose column gave fractions I (19·7 mg.), II (12·2 mg.), and III (15·8 mg.).

Fraction I was identical with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose on paper chromatography and paper ionophoresis. On crystallisation, it had m. p. 88° undepressed on admixture with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose and showed $[\alpha]_D^{18}$ +83° (equil.; *c* 0·80 in $H_2O$). The anilide (5 mg.) formed from fraction I (12 mg.) had m. p. 136° alone and in admixture with authentic *N*-phenyl-2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucosylamine.

Fraction II was identical with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose on paper chromatography and ionophoresis. The anilide (3 mg.) formed from fraction II (8 mg.) had m. p. 190° alone and in admixture with authentic *N*-phenyl-2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactosylamine.

Fraction III had $[\alpha]_D^{18}$ +60° (equil.; *c* 0·50 in $H_2O$) and was identical with 3 : 6-di-*O*-methyl-D-glucose on paper chromatography and ionophoresis and in infrared absorption spectra.

(viii) *Treatment with almond emulsin.* Trisaccharide B (20 mg.) was added to almond β-glycosidase (3 ml.). After incubation at 37° for 7 days the presence of galactose, glucose (trace), disaccharide Y, and trisaccharide B was indicated by paper chromatography. The rate of hydrolysis was similar to that of trisaccharide A.

*Characterisation of Disaccharide Y.*—(i) *Isolation.* Trisaccharide B (0·50 g.) was treated with almond emulsin (0·50 g.) in 0·05M-acetate buffer of pH 5 at 37° for 4 weeks. After fractionation on a charcoal–Celite column (*l*, 40 cm.; diam. 2 cm.), the fraction eluted with 5—6% aqueous ethanol contained disaccharide Y (69·4 mg.).

(ii) *Examination.* On paper-chromatographic and -ionophoretic examination disaccharide Y moved in the same way as disaccharide X and an authentic specimen of 2-*O*-α-D-glucopyranosyl-D-glucose. None of the three was detectable by alkaline triphenyltetrazolium chloride [10] whereas maltose, nigerose, cellobiose, lactose, and isomaltose reacted readily with this reagent. Disaccharide Y had $[\alpha]_D^{20}$ +128° (equil.; *c* 1·00 in $H_2O$).

On oxidation with alkaline hypoiodite,[8] disaccharide Y (3·0 mg.) consumed iodine equivalent to 1·54 mg. of glucose (97·5% of the theoretical value). Examined by the Shaffer–Hartmann method,[9] disaccharide Y (1·80 mg.) had a reducing power equivalent to 0·22 mg. of glucose (23% of the expected value for a disaccharide). Analyses of the complete hydrolysate of disaccharide Y showed only glucose (96% conversion).

The infrared absorption spectra of disaccharide X, disaccharide Y, and 2-*O*-α-D-glucopyranosyl-D-glucose were identical.

Disaccharide Y (8·2 mg.) with 0·05M-sodium periodate (25 ml.) consumed 3·5 moles (15 min.) and 6·05 moles (22 hr.) of periodate per mole. After 22 hr., 3·1 moles of formic acid were produced per mole.

Disaccharide Y (15 mg.) was dissolved in water (1·5 ml.), and a solution of phenylhydrazine (0·3 ml.) in 50% acetic acid (1·5 ml.) was added. The solution was heated at 100° for 1 hr. and left overnight at 0°. The osazone (5·3 mg.), after two recrystallisations from ethanol, had m. p. 196—198° undepressed on admixture with D-glucosazone.

Reduction of disaccharide Y (15·2 mg.) with sodium borohydride (16 mg.) gave disaccharide Y alcohol (12·3 mg.) which had $[\alpha]_D^{20}$ +67° (equil.; *c* 0·60 in $H_2O$). Disaccharide Y alcohol (10·5 mg.) with 0·05M-sodium periodate (10 ml.) consumed 2·85 (15 min.), 4·15 (60 min.), 4·60 (180 min.), 4·90 (1080 min.) moles per mole. After 18 hr., 2·80 moles of formic acid and 0·90 mole of formaldehyde were produced per mole.

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## 386. *Synthesis of Mycolipenic Acid.*

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The total synthesis of mycolipenic acid has been completed. (+)-2(*L*) : 4(*L*)-Dimethyldocosanoic acid * (I), an oxidation product of mycolipenic acid which has been previously synthesised,[1] was converted essentially by a route already described [2] for an optically inactive specimen into (+)-2 : 4(*L*) : 6(*L*)-trimethyltetracos-2-enoic acid (IV; R = H). The synthetic acid, regarded as the *trans*-isomer, is found to be identical with mycolipenic acid isolated from tubercle bacilli.

PREVIOUS work [1] resulted in the synthesis of (+)-2(*L*) : 4(*L*)-dimethyldocosanoic acid * (I) which proved identical with an oxidation product [3] of mycolipenic acid. It was, therefore, possible to use the oxidation product as a relay for the total synthesis of mycolipenic acid; the present paper describes this synthesis (for a preliminary report see ref. 4).

The procedure described earlier [2] for the synthesis of optically inactive 2 : 4 : 6-trimethyltetracos-2-enoic acid was followed in general. Reduction of (+)-2(*L*) : 4(*L*)-dimethyldocosanoic acid (I) with lithium aluminium hydride gave (−)-2(*L*) : 4(*L*)-dimethyldocosan-1-ol (II), $[\alpha]_D$ −6·0° (it is known [5] that an asymmetric centre adjacent to the carboxyl group is unaffected by this reduction). Condensation of the corresponding iodide, obtained *via* the toluene-*p*-sulphonyl ester, with the sodio-derivative of ethyl methylmalonate afforded by the usual successive stages (hydrolysis, decarboxylation) 2(*D*,*L*) : 4(*L*) : 6(*L*)-trimethyltetracosanoic acid (III). The resulting mixture of 2(*D*)- and 2(*L*)-diastereoisomers was used for the next stage; it is, however, of interest that the diastereoisomers were separable from each other by chromatography of their methyl esters over alumina. Bromination of the acid (III) (Hell–Volhard–Zelinsky method), followed by reaction of the α-bromo-acid bromide with methanol and dehydrobromination of the resulting α-bromo-ester by means of pyridine, gave (+)-[methyl 2 : 4(*L*) : 6(*L*)-trimethyltetracos-2-enoate] (IV; R = Me), $[\alpha]_D$ +16·4°, which from its method of preparation is regarded as the *trans*-isomer; its infrared absorption spectrum was in close agreement with that of methyl mycolipenate having $[\alpha]_D$ +16·8° (for isolation of the sample, see Experimental section). Hydrolysis of the synthetic ester afforded the corresponding acid (IV; R = H), m. p. 28°, $[\alpha]_D$ +19·3°, to be compared with m. p. 27° and $[\alpha]_D$ +19·3° for mycolipenic acid; determination of the mixed melting point and spectroscopic (ultraviolet and infrared) comparison supported their identity. The structure previously proposed [3] for mycolipenic acid is thus confirmed synthetically.

Cason and Sumrell [6] isolated from tubercle bacilli, among other products, a dextrorotatory αβ-unsaturated acid which they named "$C_{27}$-phthienoic acid." The physical data given [6,7] for this acid and its methyl ester are in close agreement with those found for

* The symbol *L* refers to the convention of Linstead, Lunt, and Weedon (*J.*, 1950, 3333).

[1] Fray and Polgar, *J.*, 1956, 2036.
[2] Bailey, Polgar, and Robinson, *J.*, 1953, 3031.
[3] Polgar and Robinson, *Chem. and Ind.*, 1951, 685; Polgar, *J.*, 1954, 1008.
[4] Millin and Polgar, *Proc. Chem. Soc.*, 1957, 122.
[5] Noyce and Denney, *J. Amer. Chem. Soc.*, 1950, **72**, 5743; see also ref. 1.
[6] Cason and Sumrell, *J. Biol. Chem.*, 1951, **192**, 405.
[7] Allen and Cason, *ibid.*, 1956, **220**, 407.

mycolipenic acid and methyl mycolipenate, and the infrared absorption spectrum [8] of methyl $C_{27}$-phthienoate does not appear to show any significant difference from that of

(I) $Me\cdot[CH_2]_{17}\cdot\overset{L}{C}HMe\cdot CH_2\cdot\overset{L}{C}HMe\cdot CO_2H$

(II) $Me\cdot[CH_2]_{17}\cdot\overset{L}{C}HMe\cdot CH_2\cdot\overset{L}{C}HMe\cdot CH_2\cdot OH$

(III) $Me\cdot[CH_2]_{17}\cdot CHMe\cdot CH_2\cdot CHMe\cdot CH_2\cdot\overset{DL}{C}HMe\cdot CO_2H$

(IV) $Me\cdot[CH_2]_{17}\cdot\overset{L}{C}HMe\cdot CH_2\cdot\overset{L}{C}HMe\cdot CH{:}CMe\cdot CO_2R$

methyl mycolipenate. However, in a recent note Cason, Urscheler, and Allen [9] express the view that $C_{27}$-phthienoic acid is not 2 : 4 : 6-trimethyltetracos-2-enoic acid: this view is mainly based on a study of a mixture of products arising on ozonisation of $C_{27}$-phthienoic acid, but there is no clear evidence on the nature of these ozonisation products, and none of them has been characterised by conversion into crystalline derivatives.

## Experimental

Ultraviolet spectra were determined for EtOH solutions, and infrared spectra for natural films. M. p.s denoted (K) were observed on the Kofler block and are corrected; all other m. p.s were determined in a capillary tube and are uncorrected. Optical rotations were measured in a 1-dm. tube except where otherwise stated. Petrol refers to light petroleum, b. p. 40—60°. The alumina used for chromatography was acid-washed, and had activity II on Brockmann and Schodder's scale.[10]

(−)-2(L) : 4(L)-*Dimethyldocosan*-1-*ol* (II).—The starting material, (+)-2(*L*) : 4(*L*)-dimethyldocosanoic acid (I), was obtained by the procedure described earlier [3] except that (i) for the oxidation with potassium permanganate the methyl esters, b. p. 231—235°/2 mm. (resulting on fractionation of the mixture of esters as described in section " Isolation of Mycolipenic Acid "), were used after removal of straight-chain esters as urea complexes, and (ii) the acidic oxidation product was subjected to chromatography over silica. The acid (970 mg.; $[\alpha]_D$ +7·1°) in ether (15 c.c.) was added dropwise with stirring to a solution of lithium aluminium hydride (430 mg.) in ether (25 c.c.) during 15 min.; the mixture was then refluxed with stirring for 3 hr. Next day the excess of lithium aluminium hydride was decomposed by dropwise addition, with stirring, of moist ether and subsequently water. Ice-cold 10% sulphuric acid (40 c.c.) was then gradually added and the ethereal layer separated; the aqueous phase was extracted with ether, and the combined ethereal extracts were washed, successively, with water, 2% aqueous sodium hydrogen carbonate, and water, then dried ($MgSO_4$), and evaporated. The residue was chromatographed in petrol on alumina (90 g.; 12 × 3 cm.) prepared in petrol. Petrol–benzene (1 : 1) eluted (−)-2(L) : 4(L)-*dimethyldocosan*-1-*ol* as a white solid (700 mg.) which crystallised from petrol at −8° as rosettes, m. p. (K) 43—45°, $[\alpha]_D^{19}$ −6·0° (*c* 4·0 in ether) (Found: C, 81·0; H, 14·1. $C_{24}H_{50}O$ requires C, 81·3; H, 14·1%).

2(DL) : 4(L) : 6(L)-*Trimethyltetracosanoic Acid* (III).—Toluene-*p*-sulphonyl chloride (500 mg.) was added in three portions during 0·5 hr. to a solution of the above alcohol (620 mg.) in dry pyridine (3·5 c.c.) at 0°, the mixture being shaken. After a further 5 hr. at <15° with occasional shaking the mixture was set aside in a refrigerator. Next day it was poured into ice-cold water, acidified with dilute hydrochloric acid, and extracted with ether. The dried ($K_2CO_3$) extract was evaporated, affording the crude toluene-*p*-sulphonate as an oil, $[\alpha]_D^{16}$ +1·80° (*c* 3·8 in ether); the infrared spectrum indicated the absence of hydroxyl and showed bands at 1190 and 1355 cm.$^{-1}$ characteristic of $-O-SO_2-$. This ester was refluxed with a solution of anhydrous sodium iodide (360 mg.) in dry acetone (5 c.c.) for 13 hr. After a further 32 hr., water was added and the product extracted with ether. The extract was washed with aqueous sodium thiosulphate and then with water, dried ($Na_2SO_4$), and evaporated, yielding the iodide (720 mg.) as an oil, $[\alpha]_D^{17}$ +3·3° (*c* 5·4 in ether; *l* 0·5). Without further purification this iodide was refluxed with the sodio-derivative of ethyl methylmalonate (from 1·25 g. of ethyl methylmalonate, 80 mg. of sodium, and 5 c.c. of ethanol) for 14 hr., and the mixture then set aside overnight. After dilution with water and acidification with hydrochloric acid the product was isolated by means of ether, then refluxed with a solution of potassium hydroxide (2·5 g.)

[8] Cason, Freeman, and Sumrell, *J. Biol. Chem.*, 1951, **192**, 415.
[9] Cason, Urscheler, and Allen, *J. Org. Chem.*, 1957, **22**, 1284.
[10] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

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in aqueous ethanol (1 : 2; 6 c.c.) for 7 hr. The resulting solution was diluted with water, acidified with hydrochloric acid, and the product, isolated by ether-extraction, decarboxylated by heating it at 160—175° (bath) for 2½ hr. The resulting acid (715 mg.) was esterified with ethereal diazomethane, and the methyl ester chromatographed in petrol on alumina (70 g.; 25 × 2 cm.) prepared in petrol. The following fractions were taken: (1) petrol (100 c.c.) (60 mg.); (2) petrol (400 c.c.) (45 mg.); (3) petrol (250 c.c.) (190 mg.); (4) petrol–benzene (9 : 1; 100 c.c.) (250 mg.); (5) petrol–benzene (9 : 1; 100 c.c.) (90 mg.); (6) petrol–benzene (9 : 1; 250 c.c.) (45 mg.); (7) benzene (300 c.c.) (trace).

Fraction (1) appeared to be essentially unchanged iodide. Fractions (3), (4), and (5), consisting of mixtures of the 2(*L*)- and 2(*D*)-diastereoisomers of the methyl ester with $[\alpha]_D^{20}$ +6·1°, +1·1°, and −1·02° (*c* 5—10 in $CHCl_3$), respectively, were combined and refluxed with 10% aqueous-ethanolic (3 : 7) potassium hydroxide (20 c.c.) for 2 hr. Acidification and ether-extraction gave the *acid* (480 mg.) as an oil which partially solidified (Found: C, 79·3; H, 12·9. $C_{27}H_{54}O_2$ requires C, 79·0; H, 13·1%).

trans-(+)-2 : 4(L) : 6(L)-*Trimethyltetracos-2-enoic Acid* (IV; R = H).—The preceding acid (480 mg.) was heated with bromine (slight excess) in the presence of red phosphorus (40 mg.) at 80—85° (bath) for 10 hr. in the manner previously described.[3] Next day anhydrous methanol (10 c.c.) was added and the mixture refluxed for 2·5 hr. Dilution with water and extraction with ether gave the crude bromo-ester which was then refluxed with dry pyridine (8 c.c.) for 19 hr. The product, isolated in the known manner, was passed in petrol over alumina. Elution with petrol (the first fractions being rejected) gave the *ester* (IV; R = Me) having $[\alpha]_D^{20}$ +16·4° (*c* 4·5 in $CHCl_3$), $n_D^{16}$ 1·4632, $\lambda_{max.}$ 2170 Å (ε 13,600). This ester and methyl mycolipenate (see below) had infrared max. at 2924, 2857, 1721, 1650, 1460, 1435, 1376, 1307, 1271, 1218, 1189, 1149, 1098, 749, and 718 $cm.^{-1}$. Hydrolysis of the synthetic ester by refluxing it with 5% methanolic potassium hydroxide, followed by acidification with hydrochloric acid, gave the *acid* which crystallised from acetone at −8° as microcrystalline rosettes, m. p. 28°, $[\alpha]_D^{21}$ +19·3° (*c* 3 in $CHCl_3$), $\lambda_{max.}$ 2160 Å (ε 13,900) (Found: C, 79·1; H, 12·5. $C_{27}H_{52}O_2$ requires C, 79·4; H, 12·8%). The acid did not depress the m. p. of natural mycolipenic acid. Its *quinine salt* crystallised from acetone at −8° as needles, m. p. (K) 87—88° (Found, after drying at 65° under vacuum for 48 hr.: C, 77·2; H, 10·4; N, 3·5. $C_{47}H_{76}O_4N_2$ requires C, 76·9; H, 10·45; N, 3·8%); upon admixture with the quinine salt (m. p. 85—86°) prepared from the naturally occurring acid the m. p. was 85—87°.

*Isolation of Mycolipenic Acid.*—The procedure described in an earlier paper [11] was employed with the following modifications. The methyl esters, fraction (b), obtained from the acids resulting on partial hydrolysis of the extracts (A) and (B), were chromatographed in petrol over silica, and the material eluted by petrol was fractionated through a Podbielniak column (75 cm.) of the concentric-tube type. The fraction, b. p. 230—230·5°/2 mm., $[\alpha]_D^{18}$ +9·82° (*c* 9·4 in ether; *l* 0·5) (0·47 g.), was dissolved in petrol (4 c.c.); urea (1·2 g.), moistened with a few drops of methanol, was added. The mixture was kept overnight; the solid was then filtered off and washed with petrol. The filtrate and washings were washed with water, dried ($Na_2SO_4$), and evaporated, affording an oil (0·38 g.) having $[\alpha]_D^{18}$ +11·55° (*c* 7·6 in ether; *l* 0·5). A further treatment with urea as above (the straight-chain ester removed as a urea complex was found to be essentially methyl hexacosanoate) left branched-chain esters (0·35 g.) with $[\alpha]_D^{18}$ +11·6° (in ether), +11·8° (in $CHCl_3$) (*c* 7·0; *l* 0·5). Repeated chromatography of this product in petrol over alumina, the first fractions eluted by petrol being rejected each time, gave methyl mycolipenate as an oil having $[\alpha]_D^{23}$ +16·8° (*c* 4·0 in $CHCl_3$), $n_D^{16}$ 1·4633, $\lambda_{max.}$ 2170 Å (ε 13,800) {Cason and Sumrell [6] record $[\alpha]_D^{20}$ +14·7°, $n_D^{25}$ 1·4600, $\lambda_{max.}$ 2180 Å (ε 12,230) for methyl $C_{27}$-phthienoate}. Hydrolysis of this ester with 5% methanolic potassium hydroxide afforded mycolipenic acid which crystallised from acetone at −8° as microcrystalline rosettes, m. p. 27°, $[\alpha]_D^{21}$ +19·3° (*c* 3 in $CHCl_3$), $\lambda_{max.}$ 2160 Å (ε 14,100). Its *quinine salt* crystallised from acetone at −8° as needles, m. p. (K) 85—86° (Found: C, 76·8; H, 10·6. $C_{47}H_{76}O_4N_2$ requires C, 76·9; H, 10·45%). Cason and Sumrell [6] and Allen and Cason [7] report several polymorphic forms for $C_{27}$-phthienoic acid, samples obtainable by low-temperature crystallisation from acetone having m. p. 26—27°; the last-named authors record for the acid $[\alpha]_D^{25}$ +19·6° ($CHCl_3$) and $\lambda_{max.}$ 2180 Å (ε 13,200 in heptane).

We thank the Medical Research Council for the award of a scholarship (to D. J. M.).

Dyson Perrins Laboratory, Oxford University. [*Received, January 14th*, 1958.]

[11] Chanley and Polgar, *J.*, 1954, 1003.

## 387. *Aromatic Alkylation. Part I.* The Kinetics of the Acid-catalysed Aralkylation by Diarylmethanols in Acetic Acid Solution.*

By D. Bethell and V. Gold.

The rate of formation of triphenylmethane derivatives by the action of diphenylmethanol on mesitylene and anisole and of 4 : 4′-dichlorodiphenylmethanol on mesitylene has been studied at 25° in a series of sulphuric acid–acetic acid mixtures with and without the deliberate addition of small amounts of water. In parallel with the kinetic measurements, the ionisation of more basic methoxydiphenylmethanols and of 4 : 4′ : 4″-tribromotriphenylmethanol in these media was examined spectrophotometrically. The kinetic orders of the reactions and the close agreement between the influence of the medium on indicator ionisation ratios and reaction velocities indicate that all the reactions studied involve a bimolecular attack of the rapidly formed diphenylcarbonium ion on the aromatic compound. Deuterium labelling at the seat of substitution does not affect the reaction velocity.

The theory of ionisation equilibria of alcohols in this solvent system is given, account being taken of the simultaneous esterification of alcohols by acetic acid. The results suggest that diphenylmethanols are appreciably esterified, whereas triphenylmethanols are not. The esterification equilibrium is established rapidly in the presence of sulphuric acid.

Westheimer and Kharasch [1] showed that the relationship between the velocity of an aromatic substitution in a series of acid media and the ionisation of primary and secondary bases in the same media could be used to identify the nature of the molecular entity responsible for attack on the aromatic molecule. Westheimer and Kharasch's study of nitration was extended,[2] especially by the late Prof. Gwyn Williams and his pupils, and the principle of the method formulated more precisely [3,4] by the definition of the acidity function $J_0$.

A similar approach has now been made to aromatic alkylation under acidic conditions. Although investigated kinetically earlier,[5] the mechanism of aromatic alkylation, under the influence of both acid and metal chloride (Friedel–Crafts) catalysts, has been inferred largely from more indirect observations, such as the nature of reaction products.[6] These studies have led to the suggestion [7] that the alkylation step of the mechanism is sometimes a bimolecular displacement reaction by the aromatic compound on an intermediate formed from the alkylating agent and the catalyst. On the other hand, it has been shown and is generally accepted that triphenylmethyl chloride acts as a triphenylmethylating agent by virtue of its ability to give rise to carbonium ions which are the effective substituting species.[8] A distinction between these two alternatives in other cases is possible by the method now reported.

First, we examined diarylmethyl compounds (such as diphenylmethanol) in acetic acid as alkylating agents towards anisole and other reactive aromatic compounds. This choice

* A preliminary summary of the present group of papers appeared in *Chem. and Ind.*, 1956, 741.

[1] Westheimer and Kharasch, *J. Amer. Chem. Soc.*, 1946, **68**, 1871.

[2] Lowen, Murray, and Williams, *J.*, 1950, 3318; Bonner, Bowyer, and Williams, *J.*, 1952, 3274; Deno and Stein, *J. Amer. Chem. Soc.*, 1956, **78**, 578.

[3] Gold and Hawes, *J.*, 1951, 2102.

[4] Gold, *J.*, 1955, 1263.

[5] *E.g.*, Olivier and Berger, *Rec. Trav. chim.*, 1926, **45**, 710; Brown and Grayson, *J. Amer. Chem. Soc.*, 1953, **75**, 6285; Lebedev, *J. Gen. Chem. U.S.S.R.*, 1954, **24**, 673; Nenitzesco, Tzitzeica, and Ioan, *Bull. Soc. chim. France*, 1955, 1272, 1279; Jungk, Smoot, and Brown, *J. Amer. Chem. Soc.*, 1956, **78**, 2185.

[6] Baddeley, *Quart. Rev.*, 1954, **8**, 355 (review).

[7] Brown and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 6292; Brown, Pearsall, Eddy, Wallace, Grayson, and Nelson, *Ind. Eng. Chem.*, 1953, **45**, 1462; Schmerling, *ibid.*, p. 1447.

[8] Hart and Cassis, *J. Amer. Chem. Soc.*, 1954, **76**, 1634; see also Bonner, Clayton, and Williams, *J.*, 1957, 2867.

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of compounds and conditions naturally restricts the scope of the conclusions reached concerning the mechanism of the Friedel–Crafts reaction. However, it was known that these conditions were particularly favourable to aralkylation in high yield [9] and without complications from olefin formation or rearrangements. Furthermore, it appears that reaction is essentially limited to attack at the *para*-position in compounds like toluene [9] or anisole.

A complication due to the use of acetic acid as solvent is the possibility of esterification of the alkylating agent by the solvent, *i.e.*,

$$R{\cdot}OH + HOAc \rightleftharpoons R{\cdot}OAc + H_2O \quad . \quad . \quad . \quad . \quad . \quad (1)$$

This reaction appears to occur only to an insignificant extent in the case of solutions of triarylmethanols, as is indicated by measurements of the ionisation of triphenylmethanol, and is to be expected from the known difficulty of esterifying these alcohols. However, some esterification is known to occur with other alcohols, including 4 : 4′-dimethoxydiphenylmethanol,[10] in acetic acid solution, and the analysis of experimental results on diarylmethyl compounds must take this reaction into account.

The present results relate to aralkylations with sulphuric acid as catalyst and the effect of addition of water upon the reaction velocity, and to related indicator measurements in the presence of these substances. In Part II the same method is applied to aralkylation under the influence of metal a halide catalyst (zinc chloride).

## Experimental

*Materials.*—Acetic acid (" AnalaR ") was dried in large batches by addition of benzene and separation of the water–benzene azeotrope and excess of benzene by fractional distillation.[11] The absence of benzene from the anhydrous acetic acid distillate (f. p. $+16{\cdot}60°$) was checked by use of the formalin–sulphuric acid reagent.[12] Anhydrous sulphuric acid was prepared by addition of sulphur dioxide-free oleum to 98% acid until the maximum freezing point was reached.

*Diphenylmethanol.* The commercial sample was purified by passage of a benzene solution through an activated alumina column and subsequent crystallisations from light petroleum (b. p. 60—80°); m. p. 67—68°. Its acetate was prepared by means of acetic anhydride in pyridine. After benzene extraction, washing, and drying, the solution of the product in light petroleum (b. p. 60—80°) was passed through an activated alumina column. Colourless crystals were obtained on removal of the solvent from the effluent. Traces of solvent were removed from the crystals of diphenylmethyl acetate (m. p. 41°) by vacuum drying.

4 : 4′-Dimethoxydiphenylmethanol was prepared by two standard methods: (*a*) by zinc-dust reduction of 4 : 4′-dimethoxybenzophenone (Eastman-Kodak Co.), or (*b*) by the reaction between the Grignard reagent of *p*-bromoanisole and anisaldehyde. In either case the product was crystallised from ether–light petroleum (1 : 1), giving silky colourless needles, m. p. 69° (lit.,[13] m. p. 72°). Repeated crystallisations failed to raise the m. p. of the product from either method of preparation.

4-Methoxydiphenylmethanol (m. p. 66—67°) was prepared in 73% yield from anisaldehyde and the Grignard reagent of bromobenzene.

4 : 4′-Dichlorodiphenylmethanol was prepared by zinc-dust reduction of 4 : 4′-dichlorobenzophenone (m. p. 91·5°; lit.,[14] m. p. 91·5°).

A pure sample (m. p. 131°) of 4 : 4′ : 4″-tribromotriphenylmethanol was kindly provided by Dr. G. L. Davies, the specimen of (−)-4-chlorodiphenylmethanol by Dr. A. G. Davies, and the specimen of [4-$^2$H]anisole by Dr. D. P. N. Satchell.

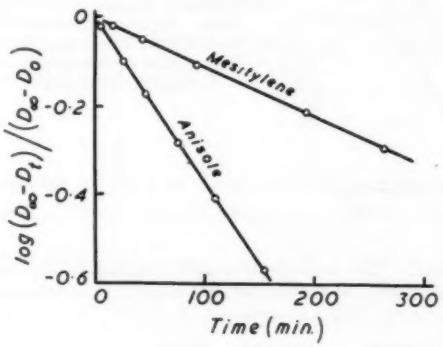
Mesitylene and anisole used in kinetic experiments were fractionally distilled commercial samples.

[9] Kundiger and Ovist, *J. Amer. Chem. Soc.*, 1954, **76**, 2501.
[10] Balfe, Kenyon, and Thain, *J.*, 1952, 790.
[11] Noyce and Castelfranco, *J. Amer. Chem. Soc.*, 1951, **73**, 4482.
[12] Feigl, " Spot Tests," Vol. II, Elsevier, Amsterdam, 1954, p. 104.
[13] Schnackenberg and Scholl, *Ber.*, 1903, **36**, 655.
[14] Norris and Tibbetts, *J. Amer. Chem. Soc.*, 1920, **42**, 209.

*Reaction Products.*—Each reaction studied kinetically is known and/or has been found to yield a single product only. Specimens of these products were prepared on a larger scale in almost quantitative yield by use of a method similar to that described by Kundiger and Ovist,[9] the conditions for which closely resemble those of the kinetic experiments. The procedure is exemplified by the preparation of 4 : 4'-dichloro-2'' : 4'' : 6''-trimethyltriphenylmethane.

**4 : 4'-*Dichloro*-2'' : 4'' : 6''-*trimethyltriphenylmethane.*** 4 : 4'-Dichlorodiphenylmethanol (2·0 g.) was added to a solution of mesitylene (12 g., tenfold excess) in a mixture of sulphuric and acetic acid (1 : 5 v/v; 150 ml.). The yellow solution rapidly reddened and was stored at room temperature for 8 days. The mixture was then poured into cold water (*ca.* 1 l.). Sodium carbonate (80 g.) was added, and the excess of mesitylene steam-distilled out of the resulting heterogeneous mixture. The residue was cooled and extracted with ether (2 × 100 ml.). Ether was distilled from the combined ethereal extracts, and some benzene was then added and distilled off the residue to dry it. Removal of this solvent left a brown oil (3·3 g.) which was dissolved in light petroleum (b. p. 80—100°) and passed through an 8 in. column of activated alumina. After removal of the solvent the product was crystallised from ethanol (pale yellow needles, 2·8 g.; 98% yield; m. p. 112—113°). Repeated crystallisations from ethanol gave colourless needles of 4 : 4'-*dichloro*-2'' : 4'' : 6''-*trimethyltriphenylmethane*, m. p. 114—115° (Found: C, 74·4; H, 5·6; Cl, 20·0. $C_{22}H_{20}Cl_2$ requires C, 74·4; H, 5·7; Cl, 20·0%).

FIG. 1.




4-Methoxytriphenylmethane (m. p. 62—63°; lit.,[15] m. p. 61°, 64·5°, 66—67°) and 2 : 4 : 6-trimethyltriphenylmethane (m. p. 119·5—120°, lit.,[9] m. p. 119—119·5°) were similarly prepared in yields of over 90%.

*Ultraviolet Absorption Spectra.*—Measurements at room temperature on a Beckman Model DU quartz spectrophotometer were used for all reactants and products, for the evaluation of ionisation ratios, and for following the progress of reactions.

*Ionisation Ratios.*—The ratio of ionised to un-ionised form, $I = [R^+]/([ROH]_{stoich} - [R^+])$, was determined in the acid mixtures by using as indicators 4 : 4' : 4''-tribromotriphenylmethanol (I), 4 : 4'-dimethoxydiphenylmethanol (II), and 4-methoxydiphenylmethanol (III). Measurements were taken at a single wavelength at or near the maximum of the carbonium-ion absorption where absorption by the un-ionised form of the indicator was negligible. The results are summarised in Tables 1, 2, and 7. The last column in Tables 1 and 2 shows that, at constant concentration of water, the measurements are consistent with the result (Ref. 3, eqn.10)

$$\log I = -2H_0 + \text{constant}$$

*Kinetic Measurements.*—Samples of the reaction mixtures were withdrawn from the thermostatically controlled (25°) reaction vessel at intervals and diluted ten-fold to arrest reaction. The optical densities of the resulting solutions were measured at a suitable wavelength, chosen by reference to the absorption spectra of the pure reactants and products. In order to reduce

[15] Bistrzycki and Herbst, *Ber.*, 1902, **35**, 3137; Kovache, *Ann. Chim.*, 1918, **10**, 201; Baeyer and Villiger, *Ber.*, 1903, **36**, 2790; Burton and Cheeseman, *J.*, 1953, 832.

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the reactions to a first-order course, the aromatic compound alkylated was generally present in large (usually ten-fold) excess over the alkylating agent. The order of the reaction with respect to the aromatic compound was established by variation of this excess. Except for very slow runs, measurements were generally taken over the first 50—80% of reaction. Rate constants were evaluated graphically from plots of log $(D_\infty - D_t)$ against $t$, where $D_\infty$ and $D_t$ are the optical densities of the diluted samples after completion of the reaction and at a time $t$ after starting the reaction, respectively. Specimen runs are illustrated in Fig. 1. The observed values of $D_0$ (the extrapolated optical density of the reaction mixture at zero time) and $D_\infty$ agreed closely with values calculated from the previously determined spectra of the reactants

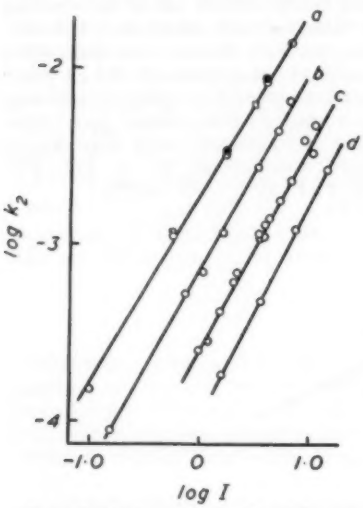


FIG. 2. *Correlation of aralkylation rates with ionisation ratios.*

*a* { Circles: Diphenylmethanol–anisole (no $H_2O$).
Squares: Diphenylmethyl acetate–anisole (no $H_2O$).
Dots: Diphenylmethanol–[4-$^2$H]anisole (no $H_2O$).
*b* Diphenylmethanol–anisole (0·55M-$H_2O$).
*c* Diphenylmethanol–mesitylene (0·55M-$H_2O$).
*d* 4 : 4′-Diphenylmethanol–mesitylene (0·55M-$H_2O$).

and products in acetic acid. The second-order rate coefficients ($k_2$) tabulated in Tables 3, 4, 5, 8, and 9 were calculated from the first-order rate constants by dividing by the concentration of aromatic compound.

TABLE 1. *Ionisation of* 4 : 4′-*dimethoxydiphenylmethanol* * (II) *in* $H_2SO_4$–AcOH.

No added water. Indicator concentration: $1·615 \times 10^{-5}$M. Wavelength of measurements ($\lambda_{max.}$): 5040 Å. $\varepsilon_{R^+} = 1·19_5 \times 10^5$.

| $H_2SO_4$ (M) | $\varepsilon$ † | log $I$ | $H_0$ ‡ | log $I + 2H_0$ | $H_2SO_4$ (M) | $\varepsilon$ † | log $I$ | $H_0$ ‡ | log $I + 2H_0$ |
|---|---|---|---|---|---|---|---|---|---|
| 0·317 | 11,210 | −0·986 | −2·29 | −5·57 | 1·546 | 103,300 | 0·796 | −3·30 | −5·80 |
| 0·711 | 55,250 | −0·068 | −2·79 | −5·51 | 1·910 | 112,600 | 1·192 | −3·46 | −5·73 |
| 1·143 | 89,800 | 0·476 | −3·11 | −5·74 | | | | | |

* The observed optical densities for this indicator did not change with time (cf. ref. 16).
† $\varepsilon$ = extinction coefficient. ‡ Taken from ref. 17.

TABLE 2. *Ionisation of* 4 : 4′ : 4″-*tribromotriphenylmethanol* (I) *in* $H_2SO_4$–AcOH.

Water concentration low and constant, but unknown. Indicator concentration: $10^{-6}$—$10^{-4}$M. Wavelength of measurements ($\lambda_{max.}$): 4720 Å. $\varepsilon_{R^+} = 91,700$.

| $H_2SO_4$ (M) | $\varepsilon$ | log $I$ | $H_0$ | log $I + 2H_0$ | $H_2SO_4$ (M) | $\varepsilon$ | log $I$ | $H_0$ | log $I + 2H_0$ |
|---|---|---|---|---|---|---|---|---|---|
| 0·632 | 874 | −2·017 | −2·71 | −7·44 | 1·974 | 22,250 | −0·494 | −3·48 | −7·45 |
| 1·017 | 3370 | −1·419 | −3·02 | −7·46 | 2·609 | 45,500 | −0·007 | −3·77 | −7·55 |
| 1·481 | 9350 | −0·945 | −3·28 | −7·51 | | | | | |

The dependence of reaction rates upon the acidity of the medium was examined from graphs of log $k_2$ against the logarithm of the ionisation ratio ($I$) of one of the diphenylmethanol-type indicators (II or III) or against Hammett's acidity function $H_0$ (in the case of experiments at

[16] Deno, Jaruzelski, and Schriesheim, *J. Amer. Chem. Soc.*, 1955, **77**, 3044.
[17] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.

constant water concentration). In both cases, rectilinear plots were obtained. In view of the observed relationship between the ionisation ratio and $H_0$ (Tables 1 and 2) the two tests are not independent. Graphs of the first type are reproduced in Fig. 2 and the slopes obtained are summarised in Table 6.

The ionisation ratios used in some of the comparisons are interpolated values based on the data of Tables 1 and 2. Although the media used for some measurements differ from some of

TABLE 3. *Rate constants for the diphenylmethylation of mesitylene at 25°.*

Concn. of added water = 0·55M. $[Ph_2CH{\cdot}OH]_{initial} = 5 \times 10^{-3}$M. [M] = initial concn. of mesitylene. $k_2$ in sec.$^{-1}$ mole$^{-1}$ l.

| $H_2SO_4$ (M) | $10^3$ [M] | $10^4k_2$ | $H_2SO_4$ (M) | $10^3$ [M] | $10^4k_2$ | $H_2SO_4$ (M) | $10^3$ [M] | $10^4k_2$ | $H_2SO_4$ (M) | $10^3$ [M] | $10^4k_2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0·729 | 3·04 | 2·59 | 0·981 | 6·03 | 6·45 | 1·162 | 7·20 | 11·3 | 1·497 | 3·04 | 23·6 |
| 0·758 | ,, | 2·92 | 0·981 | 7·53 | 6·36 | 1·233 | 3·04 | 11·3 | 1·660 | ,, | 40·3 |
| 0·871 | ,, | 4·26 | 1·008 | 3·01 | 7·08 | 1·238 | ,, | 13·3 | 1·721 | ,, | 33·8 |
| 0·981 | 3·01 | 6·20 | 1·160 | ,, | 11·3 | 1·256 | ,, | 14·5 | 1·760 | ,, | 49·1 |
| 0·981 | 4·52 | 6·17 | 1·162 | ,, | 11·2 | 1·358 | ,, | 18·3 | | | |

TABLE 4. *Rate constants for the diphenylmethylation of anisole at 25°.*

$[Ph_2CH{\cdot}OH]_{initial} = 3 \times 10^{-3}$M; $[Anisole]_{initial} = 3 \times 10^{-3}$M. $k_2$ in sec.$^{-1}$ mole$^{-1}$ l.

| (*a*) No added water | | | | (*b*) Concentration of added water = 0·55M | | | |
|---|---|---|---|---|---|---|---|
| $H_2SO_4$ (M) | $10^4k_2$ | $H_2SO_4$ (M) | $10^4k_2$ | $H_2SO_4$ (M) | $10^4k_2$ | $H_2SO_4$ (M) | $10^4k_2$ |
| 0·306 | 1·53 | 1·225 | 82·7 | 0·377 | 0·90 | 1·149 | 28·0 |
| 0·612 | 11·2 | 1·478 | 140·7 | 0·671 | 5·33 | 1·349 | 45·2 |
| 0·919 | 32·7 | | | 0·772 | 7·10 | 1·470 | 65·8 |
| | | | | 0·909 | 11·8 | | |

TABLE 5. *Rate constants for the 4 : 4′-dichlorodiphenylmethylation of mesitylene at 25°.*

Concn. of added water = 0·55M. $[Diarylmethanol]_{initial} = 0{\cdot}01$M; $[mesitylene]_{initial} = 0{\cdot}1$M.

| | | | | |
|---|---|---|---|---|
| $H_2SO_4$ (M) | 0·886 | 1·190 | 1·580 | 1·914 |
| $10^4k_2$ (sec.$^{-1}$ mole$^{-1}$ l.) | 1·87 | 4·87 | 12·53 | 27·25 |

TABLE 6. *Dependence of reaction velocity upon acidity.*

| ROH | ArH | [Added water] (M) | Table of results used | Slope (λ) of plot of log $k_2$ vs. log *I* * | Slope (λ) of plot of log $k_2$ vs. $-2H_0$ | log $k_2$ at $H_0 = -3$ |
|---|---|---|---|---|---|---|
| Diphenylmethanol | Mesitylene | 0·55 | 3 | 1·18 | 1·06 | −3·23 |
| ,, | Anisole | — | 4 (*a*) | 1·05 | 0·97 | −2·36 |
| ,, | ,, | 0·55 | 4 (*b*) | 1·11 | 1·07 | −2·77 |
| 4 : 4′-Dichlorodiphenylmethanol | Mesitylene | 0·55 | 5 | 1·24 | 1·14 | −3·60 |

* For 4 : 4′-dimethoxydiphenylmethanol as indicator.

TABLE 7. *Influence of added water on the ionisation of 4 : 4′ : 4″-tribromotriphenylmethanol* (I) *and 4-methoxydiphenylmethanol* (III).

$[H_2SO_4]_{stoich.} = 1{\cdot}428$M. Indicator concentrations: $\sim 10^{-5}$M.

| Added water (M) | | 0·0 | 0·28 | 0·55 | 1·11 | 2·78 |
|---|---|---|---|---|---|---|
| log *I* for | I | −0·07 | −0·82 | −1·22 | −1·83 | −3·17 |
| | III | −2·53 | −2·64 | −2·75 | −2·99 | −3·67 |

TABLE 8. *Influence of added water on the diphenylmethylation of anisole at 25°.*

$[H_2SO_4]_{stoich.} = 1{\cdot}428$M. $[Ph_2CH{\cdot}OH]_{initial} = 3 \times 10^{-3}$M. $[Anisole]_{initial} = 3 \times 10^{-3}$M

| Added water (M) | | 0·0 | 0·28 | 0·55 | 1·11 | 2·78 |
|---|---|---|---|---|---|---|
| $3 + \log k_2$ | | 1·096 | 1·010 | 0·903 | 0·681 | 0·054 |
| $3 + \log k_2 - \log I$ * for | I | 1·17 | 1·83 | 2·12 | 2·51 | 3·22 |
| | II | 3·63 | 3·65 | 3·65 | 3·67 | 3·72 |

* Indicator results from Table 7.

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TABLE 9. *Rate constants for diphenylmethylation of anisole by diphenylmethyl acetate.*

No added water. Temp.: 25°. $[Ph_2CH{\cdot}OAc]_{initial} = 3 \times 10^{-3}$M. $[Anisole]_{initial} = 3 \times 10^{-2}$M. $k_2$ in sec.$^{-1}$ mole$^{-1}$ l.

| $H_2SO_4$ (M) | $10^4k_2$ | log $I$ * | $H_2SO_4$ (M) | $10^4k_2$ | log $I$ * |
|---|---|---|---|---|---|
| 0·612 | 11·6 | −0·265 | 1·122 | 63·0 | 0·475 |

* Indicator ratios interpolated from results on 4 : 4′-dimethoxydiphenylmethanol (Table 1).

TABLE 10. *Diphenylmethylation of anisole and* [4-$^2$H]*anisole at* 25°.

No added water. $[Ph_2CH{\cdot}OH]_{initial} = 3 \times 10^{-3}$M. $[Anisole]_{initial} = \frac{2}{3} \times 10^{-2}$M.

| | | | |
|---|---|---|---|
| $H_2SO_4$ (M) | 0·919 | 1·225 | 1·478 |
| $10^4k_2$ for anisole | 33 | 83 | 141 |
| $10^4k_2$ for [4-$^2$H]anisole | 34 | 87 | 141 |

those used in the kinetic experiments in the (constant) amount of water present, this comparison is considered to be valid in view of the result [3] that, at different constant and low water concentrations, ionisation ratios depend upon the concentration of sulphuric acid in a fairly parallel way.

In the evaluation of the $H_0$ values of the media an allowance was made for the effect of water in reducing the acidity.[3, 11]

## DISCUSSION

The acid-catalysed formation of a triarylmethane (ArX) by reaction between diphenylmethanol (XOH) and aromatic compound (ArH) is found to be of first order with respect to both (stoicheiometric) diphenylmethanol (Fig. 1) and aromatic compound (Table 3), *i.e.*,*

$$v = -\frac{d[XOH]_{stoich.}}{dt} = k_2[XOH]_{stoich.}[ArH] \quad . \quad . \quad . \quad . \quad . \quad (2)$$

It is further found that the catalytic effect of added sulphuric acid has the same form as the effect of the acid in promoting the ionisation of an indicator (ROH) of similar structure to that of the alkylating agent XOH. For the measurements now considered ROH differed from XOH only by the presence of one or two methoxy-groups in the 4 : 4′-positions of diphenylmethanol. If the coloured form of the indicator corresponds to the cation $R^+$, the parallelism between the kinetic and indicator measurements can be expressed in the form (see Fig. 2)

$$\log k_2 = \lambda \log I + \text{constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where the constant $\lambda$ has a value close to unity (see Table 6). Inasmuch as the ionisation ratios $I$ follow a solvent property (or " acidity function ") $S$ in this medium, according to a defining relationship

$$S = \text{constant} - \log I \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

equation (3) can be stated as

$$\log k_2 = \text{constant} - \lambda S \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Hence, we conclude that the active form of the alkylating agent XOH is produced by an ionisation analogous to that of the indicator, that this active form is produced in a rapid pre-equilibrium, and that its equilibrium concentration is always low relative to that of the un-ionised form of the alkylating agent in solution.

In the absence of any esterification of the solutes ROH and XOH, the solvent property $S$ is clearly identical with the acidity function $J_0$. However, the absence of esterification cannot be assumed, and it must be left open for the present to what extent the alcohol is converted into the acetate. It may, however, be assumed that the interconversion of alcohol and acetate is rapidly established. This conclusion follows from the reproducibility and stability of the indicator spectra, from the exactness of the rate law (2) (see Fig. 1),

* Square brackets represent concentrations, and parentheses activities of the species mentioned.

and—most convincingly—from comparative alkylation measurements using diphenylmethanol and its acetate [Tables 4(*a*) and 9, and Fig. 2]. The agreement between the rates indicates that the alkylating agent is present in the same form in the two cases.

Interconversion of alcohol and acetate is rapid only when an acid catalyst is present. In the absence of catalyst the reaction is probably slow in most cases. Thus, we find that diphenylmethanol can be recovered unchanged from its solution in glacial acetic acid, and diphenylmethyl acetate can likewise be recovered from its solution. This is presumably due to the slowness of the production of diphenylcarbonium ions when the solution contains no catalyst. This result also agrees with our observation that the optical rotation of a solution of (−)-4-chlorodiphenylmethanol in glacial acetic acid remained unchanged for 43 hr. The same compound, at the same concentration (12·6 g./l.) in a 0·8M-solution of sulphuric acid in acetic acid, was completely racemised before the solution could be examined (*ca.* 10 min.).

The deductions from the kinetic and indicator measurements may be summarised in the reaction scheme

$$\left.\begin{matrix}\mathrm{XOH}\\ \mathrm{XOAc}\end{matrix}\right\} + \mathrm{H^+} \rightleftharpoons \mathrm{X^+} + \left.\begin{matrix}\mathrm{H_2O}\\ \mathrm{AcOH}\end{matrix}\right\} \text{(rapid pre-equilibrium)} \quad . \quad . \quad . \quad (6)$$

$$\mathrm{X^+ + ArH \longrightarrow ArX + H^+} \text{ (rate-controlling)} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The velocity of a reaction following this mechanism is given by

$$v = k[\mathrm{X^+}][\mathrm{ArH}]f_{\mathrm{X^+}}f_{\mathrm{ArH}}/f_{\ddagger} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where the $f$'s are activity coefficients and $f_{\ddagger}$ relates to the transition state. Combining this with the empirical rate law (2), we obtain in logarithmic notation,

$$\log k_2 = \log k - \log \frac{[\mathrm{XOH}]_{\mathrm{stoich.}}}{[\mathrm{X^+}]} + \log \frac{f_{\mathrm{X^+}}f_{\mathrm{ArH}}}{f_{\ddagger}} \quad . \quad . \quad . \quad . \quad (9)$$

According to a suggestion by Hammett, activity-coefficient ratios, in which the substances which appear in the numerator contain the same chemical fragments as the (one) substance which appears in the denominator, may reasonably be expected to be constant.[18,19] The success of applications of the Zucker–Hammett hypothesis in studies of reaction mechanism can be rationalised in terms of this principle, the limitations of which are, however, not yet known with certainty. The ratio $f_{\mathrm{ArH}}.f_{\mathrm{X^+}}/f_{\ddagger}$ is of the required form since, according to the mechanism considered, the transition state is formed from ArH and $\mathrm{X^+}$. We may therefore write

$$\log k_2 = \log k - \log ([\mathrm{XOH}_{\mathrm{stoich.}}]/[\mathrm{X^+}]) \quad . \quad . \quad . \quad . \quad (10)$$

If the extent of the conversion into carbonium ions $\mathrm{X^+}$ is small, the stoicheiometric concentration of XOH can be set equal to the sum of the actual concentrations of XOH and XOAc. The ratio $[\mathrm{X^+}]/[\mathrm{XOH}]_{\mathrm{stoich.}}$ can now be related to the ionisation ratio of the indicator by considering the hypothetical equilibria

$$\mathrm{ROH + X^+ \rightleftharpoons R^+ + XOH} \text{ (equilibrium constant } K_1) \quad . \quad . \quad . \quad (11)$$

$$\mathrm{ROAc + X^+ \rightleftharpoons R^+ + XOAc} \text{ (equilibrium constant } K_2) \quad . \quad . \quad (12)$$

$$\mathrm{ROH + XOAc \rightleftharpoons XOH + ROAc} \text{ (equilibrium constant } K_1/K_2) \quad . \quad (13)$$

Accordingly,

$$\frac{[\mathrm{XOH}]_{\mathrm{stoich.}}}{[\mathrm{X^+}]} = \frac{1}{[\mathrm{R^+}]}\frac{f_{\mathrm{X^+}}}{f_{\mathrm{R^+}}}\left\{K_1[\mathrm{ROH}]\frac{f_{\mathrm{ROH}}}{f_{\mathrm{XOH}}} + K_2[\mathrm{ROAc}]\frac{f_{\mathrm{ROAc}}}{f_{\mathrm{XOAc}}}\right\} \quad . \quad . \quad (14)$$

[18] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 276.
[19] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791.

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To simplify the problem, we shall now assume that ratios of the form

$$\frac{f_{X^+}f_{ROH}}{f_{R^+}f_{XOH}} \quad \text{and} \quad \frac{f_{X^+}f_{ROAc}}{f_{R^+}f_{XOAc}}$$

are invariant with solvent composition, and shall set them equal to unity. The first of these assumptions is, in fact, the same as the condition for the existence of a unique acidity function $J_0$ in the particular medium.[2] It has been shown that a reasonably consistent acidity function $H_0$ exists in acetic acid–sulphuric acid mixtures,[17] at any rate at low concentrations of sulphuric acid. Accordingly, we expect the function $J_0$ to be a similarly definite solvent property over the same composition range and hence consider the first assumption justified. The second ratio is of similar form and may reasonably be expected to behave analogously. It will be shown below that the constancy of $f_{X^+}f_{ROAc}/f_{R^+}f_{XOAc}$ may also formally be regarded as the condition for the existence of a related acidity function. The resultant equation can be simplified if

$$K_1 = K_2 = K_{12} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

so that

$$\frac{[XOH]_{stoich.}}{[X^+]} = K_{12}\frac{[ROH]_{stoich.} - [R^+]}{[R^+]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

This assumption requires that the position of the esterification equilibrium be the same for the reagent XOH and the indicator ROH. It leads to a result of the form of (16) and thence, on substitution in (10), to

$$\log k_2 = \text{const.} + \log \frac{[R^+]}{[ROH]_{stoich.} - [R^+]} \quad . \quad . \quad . \quad . \quad (17)$$

which is identical in form with the experimental result obtained [equation (3) and Table 6]. Simplified equations of the same form are obtained on assuming either complete or, alternatively, negligible esterification of ROH.

Assumption (15) may be regarded as reasonable when the alcohols considered are as closely related in structure as are diphenylmethanol and its *p*-chloro- and *p*-methoxy-derivatives. The esterification equilibrium is not of a kind which would be expected to be strongly dependent on polar effects of substituent groups, and steric influences are identical in the series of compounds considered.

The correlation between the kinetic and indicator measurements is shown by the agreement between the empirical constant $\lambda$ and the required value of unity (see Table 6), and this is considered to establish the proposed carbonium-ion mechanism in the present instance. This mechanism need not, however, be applicable to all types of acid-catalysed alkylations. Thus, under appropriate conditions, the initial ionisation to give $X^+$ may not be rapid relative to the speed of interaction of $X^+$ and ArH. This would lead to kinetic behaviour analogous to the "zeroth-order" reactions observed in aromatic nitration [20] or to the acid-catalysed oxygen-isotope exchange of alcohols.[21] By analogy with the suggestions of H. C. Brown and his co-workers,[7] the possible function of $XOH_2^+$ as an alkylating agent may also have to be considered. Such a mechanism would require the rate to be related to Hammett's acidity function $H_0$ according to

$$\log k_2 = \text{constant} - H_0$$

In addition to the experiments in which the acidity of the medium was varied by addition of sulphuric acid, the concentration of water in the medium being kept constant, we have examined the dependence of reaction velocity and indicator ionisation on the concentration of small amounts of added water. Gold and Hawes [3] studied the influence

[20] Benford and Ingold, *J.*, 1938, 929; Hughes, Ingold, and Reed, *J.*, 1950, 2400.
[21] Dostrovsky and Klein, *J.*, 1955, 791, 4401; Grunwald, Heller, and Klein, *J.*, 1957, 2604; Bunton, Konasiewicz, and Llewellyn, *J.*, 1955, 604.

of addition of water upon the ionisation of triphenylmethanol in mixtures of sulphuric acid and acetic acid. It was found that water represses the ionisation of triphenylmethanol more strongly than that of a Brønsted base. The effect was discussed in terms of a mass-law effect on the equilibrium

$$Ph_3C{\cdot}OH + 2H_2SO_4 \rightleftharpoons Ph_3C^+ + H_3O^+ + 2HSO_4^- \quad . \quad . \quad . \quad . \quad (18)$$

which was shown to give a reasonably successful quantitative explanation of the phenomena. Esterification of the alcohol was implicitly assumed to be negligible, as may reasonably be assumed for this particular compound. For the ionisation of a diarylmethanol, esterification must, however, be taken into account, and accordingly we observed the effect of addition of water to be markedly different for a diarylmethanol from that for a triarylmethanol indicator (Table 7). As before, the velocity of diphenylmethylation was found to parallel closely the ionisation of the diarylmethanol (Table 8).

Provided the concentration of $R^+$ is low, the effect of addition of water may be quantitatively expressed by

$$\frac{[R^+]}{[ROH]_{stoich.}} = K\frac{h_0 f_{ROH} f_{HB^+}}{(H_2O)f_{R^+}f_B}\left[1 + K_E\frac{(AcOH)f_{ROH}}{(H_2O)f_{ROAc}}\right]^{-1} \quad . \quad . \quad . \quad (19)$$

where $K$ is the equilibrium constant for the hypothetical equilibrium $H^+ + ROH \rightleftharpoons H_2O + R^+$, and $K_E$ that for reaction (1).

For the case of negligible esterification equation (19) simplifies to

$$\frac{[R^+]}{[ROH]_{stoich.}} = K\frac{h_0 f_{ROH} f_{HB^+}}{(H_2O)f_{R^+}f_B} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (20)$$

and can be rearranged to give the equations previously obtained [equation (4) of ref. 3 or equation (12) of ref. 4]. This result corresponds to the behaviour of triarylmethanols.

If there is complete esterification

$$\frac{[R^+]}{[ROH]_{stoich.}} = \frac{K}{K_E}\frac{h_0 f_{ROAc} f_{HB^+}}{(AcOH)f_{R^+}f_B} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

The significant difference between equations (20) and (21) is that the activity of water does not enter explicitly into the expression (21), so that for the case of extensive esterification, water exerts an effect only by virtue of its influence on $h_0$, the activity of acetic acid being virtually constant at low water concentrations. The change in the ratio $f_{ROAc}/f_{ROH}$ on addition of water is unknown but is expected to be of relatively minor importance.

The above analysis fits the observed behaviour of the diarylmethanol (III) at least qualitatively. At low water concentrations, addition of water produces a much smaller change on the ionisation ratio of (III) than it does on that of the triarylmethanol (I) (Table 7). This accords with the hypothesis that diarylmethanols are appreciably converted into the acetates, whereas triarylmethanols are not. However, as the water concentration (and activity) in the solution rises, the relative importance of the two terms in the last factor of equation (19) changes and, at the higher water concentrations, the effect of addition of water on the two indicators becomes gradually less different (Table 7). Thus we conclude that diarylmethanols are extensively converted into the acetates in anhydrous acetic acid but that progressively more hydrolysis takes place as water is added.

It was found (Tables 1 and 2) that for experiments at varying acidities but constant water concentration the ionisation ratios of the diarylmethanol indicator (II) and the triarylmethanol (I) changed in the same manner, the logarithms of the ionisation ratios varying as $-2H_0$. According to the discussion presented, the ionisation of the two indicators should follow equations (20) and (21) respectively. The parallel

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behaviour of the two indicators seems to indicate approximate constancy of the ratio $(AcOH)f_{ROH}/(H_2O)f_{ROAc}$ for these particular changes in the medium.

The strength of a secondary base in an aqueous acid is characterised by the constant $K$, whereas for acetic acid solutions it is the ratio $K/K_E$ which determines the ionisation tendency if there is esterification. Consequently, a direct comparison between individual differences in indicator strengths obtained in the two solvent systems is not possible.

However, according to the discussion presented, $K_E$ should have nearly the same value for different diarylmethanols. This assumption allows us to make an approximate comparison of the reactivities of the diphenylcarbonium ion and of the 4 : 4′-dichlorodiphenylcarbonium ion for reaction with mesitylene. The second-order rate constants for the alkylation of mesitylene by the two corresponding alcohols have been measured (Table 6), and $\log k_2^u/k_2^s$ varies from 0·40 to 0·32 over the range of acid concentrations studied. (The letters u and s refer to unsubstituted and substituted diphenylmethanol respectively.) According to equation (10), this logarithmic rate ratio represents

$$\log \frac{k_2^u}{k_2^s} = \log \frac{k^u}{k^s} + \log \frac{[X^+_u]}{[X_uOH]_{stoich.}} - \log \frac{[X^+_s]}{[X_sOH]_{stoich.}} \quad . \quad . \quad . \quad (22)$$

Each one of the ionisation ratios is now given by expression (21), and on making the previously mentioned assumptions we obtain

$$\log \frac{k_2^u}{k_2^s} = \log \frac{k^u}{k^s} + \log \frac{K^u}{K^s} = 0{\cdot}36 \text{ (mean experimental value)}$$

The value 0·62 can be derived for the second term on the right-hand side from reported measurements of the strengths of secondary bases,[16] so that $\log (k^u/k^s) = -0{\cdot}26$. Hence, the chloro-substituents cause a decrease in the ionisation of the alkylating agent and a slight increase in the reactivity of the intermediate carbonium ion. It is the difference in basic strengths of the alcohols which appears to govern the direction of the substituent effect in the alkylation.

The present work involves an attempt to apply the concept of acidity functions to reactions of the type

$$ROAc + H^+ \rightleftharpoons R^+ + HOAc \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (23)$$

or, more generally,

$$RX + H^+ \rightleftharpoons R^+ + HX \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (24)$$

The case of the ionisation of diphenylmethyl acetate was complicated by the necessity to include a general consideration of the incursion of equilibrium (1), but this should not be allowed to obscure the fact that the analysis presented implies that there is a solvent property (or " acidity function ") which governs ionisation reactions of acetates according to equation (23). By analogy with the definitions of $H_0$ and $J_0$ this can be expressed in the form

$$L^{OAc} = -pK_{ROAc} - \log [R^+]/[ROAc] \quad . \quad . \quad . \quad . \quad . \quad . \quad (25)$$

and the existence of the function is governed by the condition that activity-coefficient ratios of the form $f_{R^+}/f_{ROAc}$ should be independent of the nature of R in the solvent system concerned. The extension to the more general case (24) is obvious. There would not appear to be any reason to suspect that the ratio $f_{R^+}/f_{ROAc}$ should be markedly more sensitive to structure than the ratios $f_{R^+}/f_{ROH}$ and $f_{BH^+}/f_B$ although, in the general case, one might hazard the guess that the constancy of $f_{R^+}/f_{RX}$ would become a worse approximation with increasing size of X.

It is obvious that functions like $L^{OAc}$ defined above are less interesting and useful than $H_0$ and $J_0$, inasmuch as they apply to less general ionisation equilibria. However, the concept may be useful in specific cases to establish the importance of an ionisation pre-equilibrium in a particular reaction mechanism.

The relationship between $L^{OAc}$ and $H_0$ in acetic acid is evident from equation (21), and is formally analogous to that [4] between $J_0$ and $H_0$; $L_{OAc}$ and $H_0$ are clearly not very different in the dilute range considered, but this is not expected to be generally true.

The discussion in this paper has been presented without explicit consideration of ion association which is known to play an important rôle in this solvent system.[22] The simpler approach appears justified in the present case since only one anion ($HSO_4^-$) is thought to be present in the system in sufficient concentration to associate with the positively charged form of indicator and reagent. In writing $R^+$ we implicitly consider that ion to be present in association with $HSO_4^-$ ions into pairs and higher aggregates, and the activity coefficient $f_{R^+}$ to refer to a complex entity. Ultraviolet spectra [22b] do not appear to distinguish between free ions and ion pairs. The spectroscopically determined concentrations $[R^+]$ refer to gross concentrations of $R^+$ ions, *i.e.* to free ions (if any) and ions in association.

All the equations in the present paper are readily modified to conform to the notation required for a treatment in which ion-pair formation is explicitly included.[22,23] For instance, equation (19) becomes

$$\frac{[R^+HSO_4^-]}{[ROH]_{stoich.}} = \frac{K'(H_2SO_4)f_{ROH}}{(H_2O)f_{R^+HSO_4^-}}\left[1 + K_E\frac{(AcOH)f_{ROH}}{(H_2O)f_{ROAc}}\right]^{-1} \quad . \quad . \quad (26)$$

where $K'$ is now the equilibrium constant for the formation of the ion-pair $R^+HSO_4^-$ according to

$$H_2SO_4 + ROH \rightleftharpoons R^+HSO_4^- + H_2O$$

If more than one neutral acid is involved in proton donation, equation (26) is generalised to

$$\frac{\sum_i [R^+A_i^-]}{[ROH]_{stoich.}} = \sum_i\left(\frac{K'_i(HA_i)}{f_{R^+A_i^-}}\right)\cdot\frac{f_{ROH}}{(H_2O)}\left[1 + K_E\frac{(AcOH)f_{ROH}}{(H_2O)f_{ROAc}}\right]^{-1} \quad . \quad (27)$$

where the summation is over all acids $HA_i$ involved in equilibria $HA_i + ROH \rightleftharpoons R^+A_i^- + H_2O$.

It has been found that aromatic substitutions fall into two classes according to whether isotopic replacement of hydrogen at the seat of substitution has an influence upon the rate of reaction or not. The experimental study of the isotope effect in the reaction

$$Ph_2CH{\cdot}OAc + C_6H_5{\cdot}OMe \longrightarrow p\text{-}MeO{\cdot}C_6H_4{\cdot}CHPh_2 + AcOH$$

was straightforward since substitution is confined to the *para*-position in anisole, and a sample of [4-$^2$H]anisole was available from work in this laboratory on hydrogen-isotope exchange in anisole.[24] Moreover, this work had established that for the media employed deuterium replacement was a much slower reaction than aralkylation. At the concentrations of sulphuric acid used the rate of alkylation was 16—25 times greater than the rate of exchange.

The results (Table 10) indicate that the rate constants for replacement of protium and deuterium are equal within experimental error, and show that the rate-determining step of the reaction is the process $R^+ + ArH \longrightarrow RArH^+$ and that the subsequent loss of proton is kinetically insignificant. Diphenylmethylation of anisole is thus analogous to aromatic nitration, both in the mode of generation of the reactive entity in a pre-equilibrium and in the nature of the substitution step proper.

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, October 23rd,* 1957.]

[22] (*a*) Kolthoff and Bruckenstein, *J. Amer. Chem. Soc.*, 1956, **78**, 1; (*b*) Evans, Price, and Thomas, *Trans. Faraday Soc.*, 1955, **51**, 481.
[23] Satchell, following paper; Bethell, Gold, and Satchell, *J.*, 1958, 1918.
[24] Satchell, *J.*, 1956, 3911.

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## 388. *Indicator Measurements in Solutions of Hydrochloric Acid in Acetic Acid.*

By D. P. N. Satchell.

Data on the ionisation of the indicators *o*-nitroaniline, 4-chloro-2-nitroaniline, *p*-nitrodiphenylamine, and 2 : 4-dinitroaniline, in solutions of hydrogen chloride (up to *ca.* 1·8M) in anhydrous acetic acid are presented. The application of the acidity function $H_0$ to solvents other than water is discussed.

For solutions of sulphuric, phosphoric, and perchloric acid in acetic acid, considerable data on indicator ionisation exist.[1] Solutions of hydrochloric acid have, by comparison, received little attention. Measurements at three acidities around $10^{-3}$M have been given by Smith and Elliott,[2] who used two indicators and almost anhydrous acetic acid. The only other study is that of Ogata and Okano,[3] who employed a 10% aqueous solvent, one indicator, and hydrogen chloride concentrations below 1M. Results of measurements with an anhydrous solvent, four indicators, and hydrogen chloride concentrations up to 1·8M are now presented and discussed.

### Experimental

*Materials.*—Anhydrous acetic acid (m. p. >16·6°) was prepared as previously described.[4] The *o*-nitroaniline, 4-chloro-2-nitroaniline, *p*-nitrodiphenylamine,* and 2 : 4-dinitroaniline were recrystallised samples with m. p. 71·6°, 116°, 135°, and 181°, respectively. Hydrogen chloride, prepared by dehydrating a concentrated aqueous solution, was dried by bubbling it through concentrated sulphuric acid. Stock solutions of hydrogen chloride in acetic acid were made by bubbling the dried gas into the solvent. Under ordinary conditions it is difficult to obtain a concentration much above 2·0M. The stock solutions were kept in carefully sealed flasks. Their mineral acid content was found by titration for chloride by Fajans's method.

*Measurement of Ionisation Ratios.*—The indicator ionisation ratios were found by the standard methods,[5] with a Beckman spectrophotometer. Cells fitted with caps having ground surfaces were used in order to exclude moisture. Measurements were always made at the wavelengths corresponding to the maximum absorption of the basic forms of the indicators, where the ionised forms were shown to have negligible absorption. The four indicators used exist effectively completely in their basic forms in pure acetic acid: the most basic of them, *o*-nitroaniline, is less basic [3] in this solvent than is α-naphtholbenzein, a compound which has been shown to be scarcely ionised.[6] Solutions of known amounts of an indicator and hydrochloric acid were made up by volume from stock solutions, the indicator concentration always being negligible compared with that of the acid. Solutions of the indicators in acetic acid alone, and also in the presence of hydrogen chloride, were sufficiently stable to permit accurate measurements, but, particularly for *o*-nitroaniline and 4-chloro-2-nitroaniline, were not completely stable over long periods.

### Results and Discussion

As Paul and Long [5] conclude, the wide applicability of the acidity function $H_0$ to solvents other than water has still to be established. For the function to be applied unchanged (*i.e.*, with the aqueous p$K_a$ values) to other solvents, two conditions must be satisfied. First, as in water, analogous trends in ionisation must be shown by different Brønsted bases, and secondly, the relative basicities of the various bases, in these other

* Kindly supplied by Dr. V. Gold.

[1] (*a*) Paul and Hammett, *J. Amer. Chem. Soc.*, 1936, **58**, 2182; (*b*) Gold and Hawes, *J.*, 1951, 2102; (*c*) Hall and Spengeman, *J. Amer. Chem. Soc.*, 1940, **62**, 2487; (*d*) Rocek, *Chem. Listy*, 1956, **50**, 726.
[2] Smith and Elliott, *J. Amer. Chem. Soc.*, 1953, **75**, 3566.
[3] Ogata and Okano, *ibid.*, 1956, **78**, 5423.
[4] Satchell, *J.*, 1956, 3911.
[5] Paul and Long, *Chem. Revs.*, 1957, **57**, 1.
[6] Kolthoff and Bruckenstein, *J. Amer. Chem. Soc.*, 1956, **78**, 1.

solvents, must be the same as in water. If the first condition is satisfied in any solvent then obviously an acidity scale *similar* to $H_0$ may be established. It is the second condition which is critical for the generality of $H_0$ itself.

It is suggested that the evidence [1d, 7] now clearly indicates that the first condition will prove to be far more widely satisfied than the second. Maintenance of the ideal of wide generality for $H_0$, in such circumstances, can only hinder the acknowledgment of the dependence of relative basicity on medium [8] as a real phenomenon. When it proves possible to construct acidity scales in solvents other than water, no matter how similar, it seems wisest to treat all such scales as, in principle, independent, though perhaps tying them to the aqueous scale at one point, so that comparisons (more or less rough) of acidity levels may still be made.[1d, 7c]

With such a procedure the p$K_a$ values obtained in building up the various acidity scales will be those appropriate in the particular solvents concerned. Provided the medium is one in which dissociation is complete, they will be values of log $(a_{BH^+}/a_B \cdot a_{H^+})$ (with an added constant if the scale is artificially tied to the aqueous scale at some point).

If the principle of the essential independence of different scales is accepted, then, in solvents in which dissociation is incomplete, and ion-pairs are prevalent, difficulties arise concerning the exact meaning of p$K_a$ values determined by the usual step-wise procedure. In such solvents the ionisation ratios measured are of the composite type [6]

$$I_B = (\sum_i c_{BH^+A_i^-} + c_{BH^+})/c_B$$

summed over the contributions from all the acidic species, $HA_i$, present. Since the relative amounts of different acidic species in solution will, in general, change with changing acidity, it is clearly difficult, except in the special cases when only one acidic species is active, to give any simple, or useful, meaning to the p$K_a$'s obtained from ionisation data which happen to run reasonably parallel. Nor, in fact, are such data very likely to run particularly parallel in the general case for, ignoring $c_{BH^+}$, we can write

$$I_B = \sum_i a_{HA_i} \cdot f_B/K_a^{BH^+A_i^-} \cdot f_{BH^+A_i^-}$$

where $K_a^{BH^+A_i^-} = a_{HA_i} \cdot a_B/a_{BH^+A_i^-}$. Therefore, for two indicators, B and C, interacting with two acids, $HA_1$ and $HA_2$,

$$\frac{I_B}{I_C} = \frac{(a_{HA_1} \cdot f_B/K^{BH^+A_1^-} \cdot f_{BH^+A_1^-} + a_{HA_2} \cdot f_B/K_a^{BH^+A_2^-} \cdot f_{BH^+A_2^-})}{(a_{HA_1} \cdot f_C/K_a^{CH^+A_1^-} \cdot f_{CH^+A_1^-} + a_{HA_2} \cdot f_C/K_a^{CH^+A_2^-} \cdot f_{CH^+A_2^-})}$$

Even assuming that the activity coefficient ratios are compensatory, variations in acid concentration will affect $I_B/I_C$ unless the ratios $K_a^{BH^+A_1^-}/K_a^{CH^+A_1^-}$ and $K_a^{BH^+A_2^-}/K_a^{CH^+A_2^-}$ are equal. The experimental evidence already mentioned for the specific nature of relative basicity makes this unlikely to be exactly true. Hence the ionisation of different indicators will show somewhat different trends.

When, however, one ionised form of the indicators is dominant ($BH^+Cl^-$, say, for solutions of hydrogen chloride in acetic acid) then the ionisation data may reasonably be expected to show similar trends, but difficulties still remain about giving a rigorous, yet simple, meaning to the constants, because of the term $BH^+$ (and possibly terms for larger ion aggregates than pairs [6]) in the expression for $I_B$. In view of the unsatisfactory nature of media permitting ion association, from this theoretical point of view, it is suggested that the construction of acidity scales for them, in only producing ionisation constants of ill-defined meaning, serves little purpose not served by the ionisation data alone. Consequently, an acidity scale is not constructed from the data obtained in the present study.

[7] (*a*) Bunton, Ley, Rhind-Tutt, and Vernon, *J.*, 1957, 2327; (*b*) Kreevoy, *J. Amer. Chem. Soc.*, 1956, **78**, 4237; (*c*) Satchell, *J.*, 1957, 3524.

[8] Gutbezahl and Grunwald, *J. Amer. Chem. Soc.*, 1953, **75**, 559.

These data are given in the Table, from which it can be seen that the values of $\Delta \log I$ for different acid concentrations, for any given pair of the indicators, stay excellently constant. If the values of $\Delta \log I$ are taken to represent relative basicities ($\Delta pK_a$'s) of some generalised sort, say towards proton acceptance in an all-inclusive sense, then the $\Delta pK_a$'s between *o*-nitroaniline and 4-chloro-2-nitroaniline, and between 4-chloro-2-nitroaniline and *p*-nitrodiphenylamine are −0·78 and −1·39, respectively. The corresponding

*Ionisation of* (a) o-*nitroaniline*, (b) 4-*chloro-2-nitroaniline*, (c) p-*nitrodiphenylamine, and* (d) 2 : 4-*dinitroaniline, in solutions of hydrochloric acid in acetic acid at* 18° ± 2°.

| HCl (M) | 0·0029 | 0·0048 | 0·0096 | 0·0145 | 0·0195 | 0·0290 | |
|---|---|---|---|---|---|---|---|
| log $I_a$ | −0·73 | −0·39 | −0·10 | 0·06 | 0·18 | 0·36 | |
| log $I_b$ | — | — | — | −0·71 | −0·60 | −0·42 | |
| log $I_b$ − log $I_a$ | — | — | — | −0·77 | −0·78 | −0·78 | |
| HCl (M) | 0·0428 | 0·058 | 0·087 | 0·151 | 0·213 | 0·300 | 0·426 |
| log $I_a$ | 0·49 | 0·67 | | | | | |
| log $I_b$ | −0·28 | −0·13 | 0·05 | 0·27 | 0·46 | 0·61 | 0·81 |
| log $I_b$ − log $I_a$ | −0·77 | −0·80 | | | | | |
| log $I_c$ | — | — | −1·34 | −1·12 | −0·94 | −0·78 | −0·59 |
| log $I_c$ − log $I_b$ | — | — | −1·39 | −1·39 | −1·40 | −1·39 | −1·40 |
| HCl (M) | 0·592 | 0·788 | 1·18 | 1·40 | 1·67 | 1·77 | |
| log $I_b$ | 0·98 | 1·17 | 1·46 | | | | |
| log $I_c$ | −0·41 | −0·23 | 0·07 | 0·20 | 0·35 | 0·42 | |
| log $I_c$ − log $I_b$ | −1·39 | −1·40 | −1·39 | | | | |
| log $I_d$ | — | — | −1·74 | −1·61 | −1·43 | −1·38 | |
| log $I_d$ − log $I_c$ | — | — | −1·81 | −1·81 | −1·78 | −1·80 | |

values in water [5] are −0·74 and −1·45. Thus for these three compounds the change in medium, and the proximity of an anion, have little effect on their relative tendencies to accept a proton. For *p*-nitrodiphenylamine and 2 : 4-dinitroaniline the $\Delta pK_a$ in acetic acid is −1·80, compared with −2·05 in water.[5] Here there is a discrepancy comparable in magnitude with those recently found in work with other mineral acids.[1d]

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## 389. *Indicator Measurements in the Solvent Systems* $ZnCl_2$–$CH_3 \cdot CO_2H$ *and* $ZnCl_2$–HCl–$CH_3 \cdot CO_2H$.

By D. BETHELL, V. GOLD, and D. P. N. SATCHELL.

The ionisation ratios of Brønsted bases and of 4 : 4′-dimethoxydiphenylmethyl compounds in solutions of zinc chloride in acetic acid increase with rising zinc chloride concentration. In the presence of hydrogen chloride the ionisation ratios pass through a maximum, decrease to a minimum, and then rise again, as the concentration of zinc chloride is raised. The measurements are interpreted as reflecting corresponding changes in the acidity (in the Brønsted–Lowry sense) of the media. The characteristic dependence of the ionisation ratios upon zinc chloride concentration is attributed to two different forms of chemical interaction between zinc chloride and hydrogen chloride. Secondary differences in behaviour between the two types of indicator are discussed.

To complement kinetic studies * on aromatic alkylation [1] and hydrogen-isotope exchange [2] in the systems $ZnCl_2$–$CH_3 \cdot CO_2H$ and $ZnCl_2$–HCl–$CH_3 \cdot CO_2H$, the ionisation of various indicators in these media has been investigated. The compositions of the media were such that acetic acid always constituted the largest component, acting both as solvent for

* See following papers.

[1] Bethell and Gold, *J.*, 1958, 1930.
[2] Satchell, preceding paper.

the other species and as a potential Brønsted acid. No previous studies of indicator ionisation in the presence of both Lewis and Brønsted acids have been reported, though the high level of acidity often shown by such combinations is well known from other work.[3]

Three kinds of indicator were used: (1) Brønsted base indicators of the type used by Hammett in his studies with strongly acidic media;[4] (2) 4 : 4′-dimethoxydiphenylmethyl compounds; (3) (for a few measurements) triphenylmethyl chloride. The nature of the equilibria in which these substances engage in the present media is now discussed.

1. *Brønsted Base Indicators.*—(i) *Solvent system* $ZnCl_2$–$CH_3{\cdot}CO_2H$. The ionisation of four of the indicators usual in acidity-function studies,[4] namely, *p*-nitroaniline, *o*-nitroaniline, 4-chloro-2-nitroaniline, and *p*-nitrodiphenylamine, was investigated. The last three exist solely in their basic forms in pure acetic acid.[5] Solutions of the more basic *p*-nitroaniline in the pure solvent have finite absorption at the wavelength of maximum absorption of the ionised form. It is difficult to decide whether this absorption is due to the ionised or the un-ionised form by direct experiment, because added bases (*e.g.*, sodium acetate) will have no effect on equilibria of the type [6]

$$B + AcOH \rightleftharpoons \overset{+}{B}H\overset{-}{O}Ac \quad \text{(ion pair)}$$

However, it is known [6] that *p*-naphtholbenzein † is not detectably ionised in acetic acid, and since this compound is not much less basic than *p*-nitroaniline it follows that *p*-nitroaniline itself can only be negligibly ionised. This conclusion is supported by results to be discussed below.

When anhydrous zinc chloride is added to a solution of one of the aforementioned indicators in acetic acid, the absorption spectrum of the indicator changes gradually from that of the basic form to that characteristic of the ionised, or acidic, form, as on addition of Brønsted acids such as hydrogen chloride or sulphuric acid. Measurement of indicator ratios, *I* (ratio of acidic to basic form), at various zinc chloride concentrations, is thus possible. This colour change of the indicators is considered to be a manifestation of their basicity in the Brønsted sense, *i.e.*, the indicators are thought to receive a proton, rather than to be involved in any direct interaction with zinc chloride.[2]

For solutions of the common mineral acids in acetic acid, plots of log *I* against acid concentration for different indicators of the type under consideration have constant separations.[7] However, for two given indicators the exact separations may depend on the mineral acid involved and may also differ from those found when water is the solvent. These discrepancies imply different relative basicities for the indicators in the different systems.[5]

The present system and indicators show behaviour analogous to that found with mineral acids.[5,7] The plots of log *I* against the logarithm of the zinc chloride concentration (Fig. 1) provide a set of curves with reasonably constant separations, though *p*-nitrodiphenylamine shows some individual tendency. The behaviour of *p*-nitroaniline conforms with that of the other indicators, and this is additional circumstantial evidence for the assumption that this compound is effectively un-ionised in the pure solvent.

If the separations of the plots are taken to represent the relative basicities of the indicators, then the $\Delta pK_a$'s between *p*-nitroaniline and *o*-nitroaniline, between *o*-nitroaniline and 4-chloro-2-nitroaniline, and between 4-chloro-2-nitroaniline and *p*-nitrodiphenylamine are −1·66, −0·95, and −1·22, respectively. The values in water are −1·28,

† *p*(or α)-Naphtholbenzein is a secondary base and in dissociating solvents may therefore respond to the $J_0$ function rather than to $H_0$ (cf. refs. 6, 14).

[3] *E.g.*, McCauley and Lien, *J. Amer. Chem. Soc.*, 1951, **73**, 2013; Kilpatrick and Luborsky, *ibid.*, 1953, **75**, 577; Brown and Brady, *ibid.*, 1952, **74**, 3570; Brown and Wallace, *ibid.*, 1953, **75**, 6268.
[4] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co. Inc., New York, 1940.
[5] Satchell, *J.*, 1958, 1916.
[6] Kolthoff and Bruckenstein, *J. Amer. Chem. Soc.*, 1956, **78**, 1.
[7] Paul and Hammett, *ibid.*, 1936, **58**, 2182; Hall and Spengeman, *ibid.*, 1940, **62**, 2487; Roček, *Chem. Listy*, 1956, **50**, 726.

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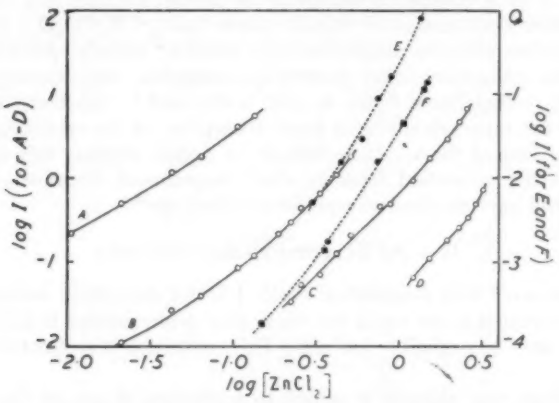
—0·74, and —1·45 respectively.[8] Comparisons for the mineral acids in acetic acid show similar discrepancies.[5,7] A comparison of the present data with those obtained for solutions of hydrogen chloride in acetic acid [5] shows that, for all the indicators common to both studies, the amount of ionisation produced by a given concentration of zinc chloride

FIG. 1. *Indicator ionisation in* $ZnCl_2$–$CH_3{\cdot}CO_2H$.




*A*: *p*-Nitroaniline. *B*: *o*-Nitroaniline. *C*: 4-Chloro-2-nitroaniline.
*D*: *p*-Nitrodiphenylamine. *E*: Triphenylmethyl chloride.
*F* { ● 4 : 4′-Dimethoxydiphenylmethyl chloride.
■ 4 : 4′-Dimethoxydiphenylmethanol.

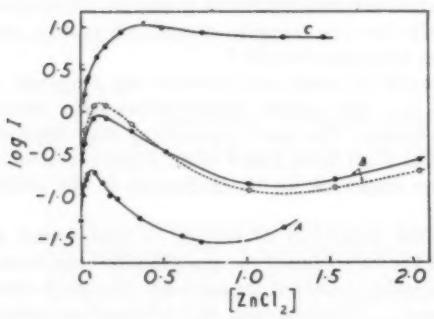



FIG. 2. *Ionisation of Brønsted bases in* $ZnCl_2$–HCl–$CH_3{\cdot}CO_2H$.

*A*: [HCl] = 0·013M.
*B*: [HCl] = 0·05M.
*C*: [HCl] = 0·42M.

●, 4-Nitrodiphenylamine.
○, 4-Chloro-2-nitroaniline.

is much less than that brought about by the same stoicheiometric concentration of hydrogen chloride (Table 2). Thus the general level of acidity is much higher in the presence of hydrogen chloride.

(ii) *Solvent system* $ZnCl_2$–HCl–$CH_3{\cdot}CO_2H$. Measurements were made of the changes in indicator ionisation when increasing amounts of zinc chloride were added to acetic acid containing a constant quantity of hydrogen chloride. Three hydrogen chloride concentrations (0·013, 0·05, and 0·42M) were investigated, *p*-nitrodiphenylamine being used throughout. In the solutions containing 0·05M-hydrogen chloride, measurements were also made with 4-chloro-2-nitroaniline. Plots of log *I* against zinc chloride concentration are shown in Fig. 2. The shapes of the curves are very different from those obtained when either hydrogen chloride [5] or zinc chloride is used alone. The addition of small amounts

[8] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.

of zinc chloride to a constant quantity of hydrogen chloride markedly increases the ionisation—an increase much greater than that expected if the contributions of zinc chloride and hydrogen chloride [5] were simply additive. With further addition of zinc chloride the acidity passes through a maximum and a minimum, the positions of which depend on the hydrogen chloride concentration. (The increase in ionisation achieved at the maxima of the curves is roughly the same at each hydrogen chloride concentration, and amounts to a change in log $I$ of about 1·5 units.)

Even when only one acidic species is present in solution the ionisation trends of different indicators are not always parallel.[5,7,8] In the present solutions it seems likely (as is argued more fully later) that more than one Brønsted acid is active and this is an additional and special reason for expecting such discrepancies.[5] The broken curve in Fig. 2 is a plot of log $I$ − 1·45 for 4-chloro-2-nitroaniline at 0·05M-hydrogen chloride. Its general shape is very similar to that of the plot for *p*-nitrodiphenylamine at the same concentration, but detailed parallelism is lacking.

(iii) *Nature of the chemical species responsible for the ionisation.* The observed variations in indicator ionisation lead to the following conclusions.

(*a*) When zinc chloride is present alone there is at least one type of interaction with the solvent which results in the formation of an additional Brønsted acid species. This is quite plausible in view of the existence of compounds such as $BF_3,2CH_3 \cdot CO_2H$. As has been previously mentioned, the ionisation curves in the presence of zinc chloride alone are similar to those obtained when a single mineral acid is used in this solvent. Thus, for these solutions the simplest interpretation is that zinc chloride is engaged in a single equilibrium with the solvent.

(*b*) When both hydrogen chloride and zinc chloride are present at least two further acidic complexes must be formed, and there is, in fact, some previous evidence of complex formation, of some kind, between zinc chloride and hydrogen chloride in both aqueous [9] and acetic acid [10,11] solutions.

Unless *two* further acidic species are postulated it does not seem possible to explain the increase *and* subsequent decrease in ionisation. An alternative explanation of the decrease as due to deactivation of the indicators by complex formation with zinc chloride, is unlikely to be correct, since the phenomenon also occurs with indicators of a different type (see p. 1923) and in the exchange reaction with anisole [2] (see following paper), a compound for which ultraviolet absorption measurements show no evidence of complex formation.[1]

The ionisation maximum does not occur at a composition corresponding to any simple, or constant, stoicheiometry; in the range of hydrogen chloride concentrations studied it occurs when the concentration of zinc chloride is 1—5 times greater than that of the hydrogen chloride. Similarly, the positions of the acidity minima do not correspond to a fixed stoicheiometric ratio. These facts strongly imply the operation of mass-law effects in the interactions between hydrogen chloride and zinc chloride.

Specific chemical interpretation of the various forms of interaction between zinc chloride, hydrogen chloride, and acetic acid is handicapped by the paucity of modern work on the chemistry of zinc complexes in solution. In the solid state a large number of double salts of zinc halides have been reported and structural evidence indicates the considerable stability of the tetrahedral ion $ZnCl_4^{2-}$ and a general preference for four-co-ordinated structures.[12] By analogy, it seems likely that four-fold co-ordination gives rise to the most stable complexes in solution also, though there is evidence for the existence of both $ZnCl_3^-$ and $ZnCl_4^{2-}$ from Raman spectra of potassium chloride–zinc chloride melts,[13] where the three-fold co-ordination cannot be supplemented by solvent molecules.

The preference for four-fold co-ordination being borne in mind, the following suggestions

[9] Hildebrand and Bowers, *J. Amer. Chem. Soc.*, 1916, **38**, 785.
[10] Davidson and Chappell, *ibid.*, 1939, **61**, 2164.
[11] Andrews and Keefer, *ibid.*, 1956, **78**, 4549, 5623; 1957, **79**, 4348.
[12] Bailar, "Chemistry of Co-ordination Compounds," Reinhold Publishing Co., New York, 1956.
[13] Bues, *Z. anorg. Chem.*, 1955, **279**, 104.

are thought to represent the simplest chemical interpretations of the present ionisation data.

In solutions of zinc chloride alone, the single equilibrium postulated is

$$ZnCl_2 + 2AcOH \rightleftharpoons H_2ZnCl_2(OAc)_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

the complex acid being responsible for the observed acidic effects. It seems reasonable to suppose that co-ordinated acetic acid will possess enhanced acidity, since the attachment of the electron-pair acceptor molecule will withdraw electrons from acetic acid. Zinc chloride is stable in acetic acid,[10] so that solvolysis to give some hydrogen chloride is not an alternative explanation.

When both zinc chloride and hydrogen chloride are present in the solvent the following equilibria seem the most likely:

$$2HCl + H_2ZnCl_2(OAc)_2 \rightleftharpoons H_2ZnCl_4 + 2AcOH \quad . \quad . \quad . \quad . \quad (2)$$

$$H_2ZnCl_4 + H_2ZnCl_2(OAc)_2 \rightleftharpoons 2H_2ZnCl_3(OAc) \quad . \quad . \quad . \quad . \quad (3)$$

An alternative to the complex $H_2ZnCl_3(OAc)$, having the same $ZnCl_2$ : HCl ratio, is $H_2Zn_2Cl_6$ with four-fold co-ordination achieved by a bridge structure similar to that in $Al_2Cl_6$. However, no such structure has previously been indicated for zinc compounds. A further possibility, with a higher $ZnCl_2$ : HCl ratio, would be $H^+[ZnCl]^+[ZnCl_4]^{2-}$.

In terms of the above equilibria the qualitative explanation of the observed ionisation curves is as follows. When zinc chloride is added to a solution of hydrogen chloride in acetic acid the initial, sharp increase in acidity is to be attributed to the species $H_2ZnCl_4$, though this acid cannot be formed quantitatively since maximum ionisation occurs at a zinc chloride concentration greater than that corresponding to the ratio $ZnCl_2$ : HCl = 1 : 2. As more zinc chloride is added the acidity falls, and therefore $H_2ZnCl_4$ is clearly being replaced by a weaker acid with a higher $ZnCl_2$ : HCl ratio, and having one of the formulæ indicated above. The formula $H_2ZnCl_3(OAc)$ seems the most likely, being intermediate in structure between $H_2ZnCl_4$ and $H_2ZnCl_2(OAc)_2$. The latter species will become increasingly important with further addition of zinc chloride, and accounts for the gradual recovery of acidity.

It is possible, on the above basis, to deduce an expression for $I$ in terms of the various equilibrium constants and the stoicheiometric concentrations of hydrogen chloride and zinc chloride, but the equation is too complex to be of practical quantitative value.

The high acid strength of $H_2ZnCl_4$ calls for some comment. At the maximum of the ionisation curves there is certainly less $H_2ZnCl_4$ present than corresponds to the stoicheiometric hydrogen chloride concentration. Comparison of the ionisation produced with that produced by other acids in acetic acid [14] leads to the deduction that $H_2ZnCl_4$, in this solvent, is a stronger acid than perchloric, and probably stronger than any acid previously studied. It is, therefore, likely to be fairly completely ionised, since Kolthoff and Bruckenstein [6] give the ionisation constant for perchloric acid as unity.

Concerning the detailed structures of the complex acids—structures which must plausibly account for the differences in acidity—two views are possible. First, it may be assumed that in both $H_2ZnCl_4$ and $H_2ZnCl_3(OAc)$, all the hydrogen originating from the hydrogen chloride is completely ionised, giving ion-pairs or clusters of the type $2H^+[ZnCl_4]^{2-}$ and $H^+[ZnCl_3(AcOH)]^-$. The marked differences in strength between the two acids would then have to be attributed to the differences in the positions of the following equilibria involving the Brønsted base B:

$$B + 2H^+[ZnCl_4]^{2-} \rightleftharpoons BH^+[H]^+[ZnCl_4]^{2-} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$B + H^+[ZnCl_3(AcOH)]^- \rightleftharpoons BH^+[ZnCl_3(AcOH)]^- \quad . \quad . \quad . \quad . \quad (5)$$

[14] Smith and Elliott, *J. Amer. Chem. Soc.*, 1953, **75**, 3566.

*i.e.*, it is necessary to postulate that equilibrium (4) lies much further to the right than equilibrium (5). In this scheme the hydrogen of the co-ordinated acetic acid molecules is regarded as only partially ionised.

Alternatively, it may be assumed that even the hydrogen originating from the hydrogen chloride is only partially ionised in the weaker acid. On this basis the relative strengths can be thought of as determined largely by the relative amounts of ionisation, which in turn would be determined by the relative stabilities of the ions $[ZnCl_4]^{2-}$, $[ZnCl_3(OAc)]^{2-}$, and $[ZnCl_2(OAc)_2]^{2-}$. These are certainly likely to be different, with $[ZnCl_4]^{2-}$ the most stable. The difficulty of this interpretation is to formulate an acceptable structure for the un-ionised species $H_2ZnCl_3(OAc)$ (or any of its alternatives considered). However, analogous problems exist in other cases.[15] The proton of the species $H[ZnCl_3(AcOH)]$ cannot be donated, in any way, to the complexed acetic acid molecule, since this molecule must be regarded as more acidic and less basic than the uncomplexed solvent, which will therefore receive a proton preferentially. The possibility of appreciable solvation or hydrogen bonding of incipiently ionised protons may be the governing factors for the formation of hydrogen halide–Lewis acid complexes, for there is evidence that, by themselves, boron trifluoride and hydrogen fluoride do not interact to form a significant amount[16] of $HBF_4$. Even in the present system it is not necessary to assume that the acids $H_2ZnCl_4$ and $H_2ZnCl_2(OAc)_2$ are capable of independent existence. The ions $[ZnCl_4]^{2-}$ (and $[ZnCl_2(OAc)_2]^{2-}$) need only be formed on the addition of a base (B), according to

$$2B + ZnCl_2 + 2HCl \rightleftharpoons 2BH^+[ZnCl_4]^{2-} \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

However, it is essential to the explanation of the ionisation maximum to assume that some hydrogen chloride is actually bound to zinc chloride to form the intermediate (and less acidic) complex [of formula $H_2ZnCl_3(OAc)$ or one of its alternatives] in acetic acid solution. Such a compound must therefore exist, in spite of our present inability to give it an entirely satisfactory structural formula. The similar difficulties of formulation of $H_2ZnCl_4$ and $H_2ZnCl_2(OAc)_2$ are therefore no evidence against the existence of these compounds.

2. *The Indicators* 4 : 4′-*Dimethoxydiphenylmethanol* (P), *its Chloride* (Q), *and Triphenylmethyl Chloride* (R).—(i) *Solvolysis of the indicators.* It has previously been shown[17] that dissolution of a small quantity of a diarylmethanol in sulphuric acid–acetic acid media results in a rapid conversion into the corresponding acetate. It seems reasonable to assume that a similar acid-catalysed reaction occurs in acetic acid rendered more acidic by the presence of zinc chloride. Solvolysis also occurs when a chloride, such as Q, is dissolved in acetic acid containing zinc chloride, as is indicated by the ultraviolet spectra of diphenylmethyl acetate. In the presence of a little zinc chloride, which for these compounds produces a spectrometrically undetectable amount of ionisation, both compounds give the spectrum characteristic of the acetate in the pure solvent.[1]

It may be concluded that, in the presence of zinc chloride, the solution of a diarylmethyl chloride will result in an equilibrium mixture of the alcohol, chloride, and acetate, with the last predominating. When both hydrogen chloride and zinc chloride are present initially in the solvent, dissolution of the alcohol will produce all three species, the acetate predominating though the amount of chloride present at equilibrium may depend on the concentration of hydrogen chloride. However, formation of an appreciable amount of diarylmethyl chloride is unlikely at the concentrations examined.[17] Triphenylmethyl chloride (R) is not substantially solvolysed in acetic acid.[18]

(ii) *Solvent system* $ZnCl_2$–$CH_3{\cdot}CO_2H$. In this system measurements were made with

[15] Olah, Kuhn, and Olah, *J.*, 1957, 2174; Brown, Pearsall, Eddy, Wallace, Grayson, and Nelson, *Ind. Eng. Chem.*, 1953, **45**, 1462.
[16] Kilpatrick and Luborsky, *J Amer Chem. Soc.*, 1954, **76**, 5865.
[17] Bethell and Gold, *J.*, 1958, 1905.
[18] Evans, Price, and Thomas, *Trans. Faraday Soc.*, 1955, **51**, 481.

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both the alcohol (P) and the chloride (Q) form of the diphenylmethyl indicator. The observed ionisation ratios for both compounds fall on the same curve (Fig. 1), as is to be expected if solvolysis of the chloride is rapid and practically complete, and the indicator concentration low, so that the hydrogen chloride produced in the solvolysis is present only to an insignificant extent. As for the Brønsted bases, increasing amounts of zinc chloride produce a steady increase in indicator ionisation, and at all zinc chloride concentrations the ionisation is much less than that produced by the same concentration of sulphuric acid; triphenylmethyl chloride (R) responds similarly to the addition of zinc chloride to the solution (Fig. 1).

(iii) *Solvent system* $ZnCl_2$–HCl–$CH_3{\cdot}CO_2H$. The ionisation of indicator P was again studied for increasing concentrations of zinc chloride in solutions containing a fixed concentration of hydrogen chloride (Fig. 3). Although the small number of experimental

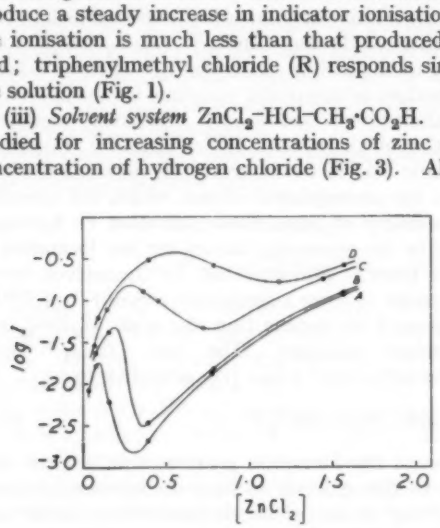


FIG. 3. *Ionisation of* 4 : 4′*-dimethoxydiphenylmethyl chloride in* $ZnCl_2$–HCl–$CH_3{\cdot}CO_2H$.

*A*: [HCl] = 0·0099M.
*B*: [HCl] = 0·016M.
*C*: [HCl] = 0·027M.
*D*: [HCl] = 0·054M.

points allows some latitude in the drawing of the curves, it is evident that the maximum–minimum effects shown by the Brønsted bases (Fig. 2) are also displayed by this indicator. The parallelism is not exact, as the maxima now occur at larger concentrations of zinc chloride. The similarities of the curves suggest that the ionisation of P is largely, but not entirely, governed by the proton-donating power of the solution, and that the colour change is not due to direct association of zinc chloride with P.

(iv) *Differences between Brønsted bases and secondary bases.* The ionisation of the diarylmethanol–diarylmethyl acetate system under the influence of an acid catalyst in acetic acid has been discussed in a preceding paper.[17] For the case where the acetate is the predominant un-ionised form of the indicator, the ionisation ratio may be expressed in the form (ion-pair dissociation and the formation of higher aggregates being neglected)

$$I = \frac{\sum_i [R^+A_i^-]}{[ROAc]} = \sum_i \frac{K_i'}{K_E} \frac{(HA_i)\, f_{ROAc}}{(AcOH)\, f_{R^+A_i^-}} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where the symbols have the significance previously defined,[17] the ratio $K_i'/K_E$ also being the equilibrium constant for the reaction

$$ROAc + HA_i \rightleftharpoons R^+A_i^- + AcOH \quad . \quad . \quad . \quad . \quad . \quad (8)$$

For the Brønsted base indicators (B) previously discussed

$$I = \sum_i \frac{[BH^+A_i^-]}{[B]} = \sum_i \frac{(HA_i)}{K_a^{BH^+A_i^-}} \cdot \frac{f_B}{f_{BH^+A_i^-}} \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where $K_a^{BH^+A_i^-}$ is the equilibrium constant for the reaction

$$BH^+A_i^- \rightleftharpoons B + HA_i \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

Comparison of equations (7) and (9) reveals that they are of similar form, the most significant difference being the appearance of the activity of acetic acid in the denominator of (7). This difference is the same as that found for the two types of indicator in the system sulphuric acid–acetic acid and which was expressed [17]—without explicit consideration of ion association—as the difference between two "acidity functions" ($H_0$ and $L^{OAc}$). It is, therefore, intelligible that the ionisation ratios of the two types of indicator should show qualitatively the same sort of dependence on zinc chloride and hydrogen chloride concentration, but that there should be quantitative differences. If zinc chloride reduces the activity of acetic acid the maxima in the curves of Fig. 3 should be displaced towards higher zinc chloride concentrations than are found in Fig. 2 and the minima towards lower ones, as is observed. Furthermore, the detailed shapes of the various curves are likely to be very sensitive to small quantities of water in the solvent, since these may induce the acids to dissociate and will affect the alcohol–acetate–chloride equilibria for the secondary bases.

A more complex formula than (7) is obviously required for an indicator whose equilibrium mixture contains appreciable concentrations of alcohol and chloride, and may be obtained by an obvious elaboration of equation (4) in ref. 17.

## Experimental

*Materials.*—Anhydrous acetic acid, hydrogen chloride, and stock solutions of the latter in the former were prepared as previously described.[5]

The anhydrous zinc chloride was supplied as fused sticks (B.D.H). Stock solutions of zinc chloride in acetic acid were made by dissolving sticks, the surfaces of which had first been washed in a separate portion of the anhydrous solvent. The sticks contain a little insoluble impurity and stock solutions were centrifuged to remove this. The compositions of the hydrogen chloride and zinc chloride solutions were determined by titration for chloride, by using either Fajans's or a modified Volhard procedure.

The *p*-nitroaniline, *o*-nitroaniline, 4-chloro-2-nitroaniline, and *p*-nitrodiphenylamine were recrystallised samples with m. p. 148°, 71·6°, 46°, and 135°, respectively.

4 : 4′-Dimethoxydiphenylmethanol was the specimen used in earlier work.[17] 4 : 4′-Dimethoxydiphenylmethyl chloride was prepared by passing a stream of hydrogen chloride through the ethereal solution of the alcohol and removing the water formed at several stages. After being dried ($CaCl_2$) the solution was neutralised (anhyd. $Na_2CO_3$) and filtered. The ether was distilled off and the colourless residue recrystallised from ether at a low temperature (m. p. 83—84). Triphenylmethyl chloride was a recrystallised commercial specimen.

*Measurements of Ionisation Ratios.*—The general procedure has been described before.[5, 17] The solutions containing known amounts of indicator, hydrogen chloride, and zinc chloride were made up, by volume, from stock solutions. The *p*-nitroaniline solutions were unstable, but not sufficiently so to prevent accurate measurements being made by a short extrapolation to zero time.

Table 1. *Ionisation of* (a) p-*nitroaniline*, (b) o-*nitroaniline*, (c) 4-*chloro*-2-*nitroaniline*, *and* (d) p-*nitrodiphenylamine in solutions of zinc chloride in acetic acid at* 18° ± 2°.

| $ZnCl_2$ (M) | 0·0106 | 0·0212 | 0·0424 | 0·0636 | 0·106 | 0·133 | | |
|---|---|---|---|---|---|---|---|---|
| log $I_a$ | −0·67 | −0·31 | +0·06 | 0·25 | 0·61 | 0·74 | | |
| log $I_b$ | | −1·96 | −1·58 | −1·41 | −1·08 | −0·93 | | |
| log $I_b$ − log $I_a$ | | −1·65 | −1·64 | −1·66 | −1·69 | −1·67 | | |
| $ZnCl_2$ (M) | 0·186 | 0·222 | 0·255 | 0·333 | 0·420 | 0·510 | 0·765 | |
| log $I_b$ | −0·67 | −0·53 | −0·36 | −0·19 | +0·04 | +0·26 | | |
| log $I_c$ | | −1·47 | −1·28 | −1·16 | −0·91 | −0·69 | −0·34 | |
| log $I_c$ − log $I_b$ | | −0·94 | −0·92 | −0·97 | −0·95 | −0·95 | | |
| $ZnCl_2$ (M) | 0·888 | 1·21 | 1·53 | 1·95 | 2·30 | 2·55 | 2·87 | 3·19 |
| log $I_c$ | −0·31 | −0·03 | +0·23 | 0·46 | 0·67 | 0·83 | | |
| log $I_d$ | | −1·19 | −0·96 | −0·74 | −0·59 | −0·47 | −0·31 | −0·14 |
| log $I_d$ − log $I_c$ | | −1·16 | −1·19 | −1·20 | −1·26 | −1·30 | | |

TABLE 2. *Ionisation of* 4-*chloro*-2-*nitroaniline in acetic acid in the presence of* (a) *hydrogen chloride*, (b) *zinc chloride, at rounded molarities at* 18° ± 2°.

| HCl (or $ZnCl_2$) (M) | 0·2 | 0·4 | 0·6 | 0·8 | 1·0 | 1·2 |
|---|---|---|---|---|---|---|
| log *I* (*a*) | +0·42 | 0·78 | 1·01 | 1·19 | 1·34 | 1·48 |
| log *I* (*b*) | −1·56 | −0·96 | −0·60 | −0·33 | −0·18 | −0·03 |

TABLE 3. *Ionisation of* (a) p-*nitrodiphenylamine and* (b) 4-*chloro*-2-*nitroaniline in acetic acid containing both hydrogen chloride and zinc chloride, at* 18° ± 2°.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (i) HCl = 0·013M | | | | | | | |
| $ZnCl_2$ (M) | 0·0 | 0·0044 | 0·0133 | 0·0222 | 0·0355 | 0·044 | 0·088 |
| log $I_a$ | −2·13 * | −1·39 | −0·98 | −0·88 | −0·81 | −0·75 | −0·73 |
| $ZnCl_2$ (M) | 0·132 | 0·176 | 0·220 | 0·352 | 0·610 | 0·720 | 1·22 |
| log $I_a$ | −0·85 | −1·00 | −1·04 | −1·27 | −1·48 | −1·55 | −1·38 |
| (ii) HCl = 0·05M | | | | | | | |
| $ZnCl_2$ (M) | 0·0 | 0·010 | 0·026 | 0·077 | 0·153 | 0·306 | 0·510 |
| log $I_a$ | −1·60 * | −0·58 | −0·38 | −0·08 | −0·08 | −0·23 | −0·48 |
| log $I_b$ | −0·21 * | +1·07 | 1·23 | 1·52 | 1·52 | 1·30 | 0·97 |
| $ZnCl_2$ (M) | 1·02 | 1·53 | 2·04 | | | | |
| log $I_a$ | −0·86 | −0·81 | −0·56 | | | | |
| log $I_b$ | 0·51 | 0·54 | 0·75 | | | | |
| (iii) HCl = 0·42 (M) | | | | | | | |
| $ZnCl_2$ (M) | 0·0 | 0·0244 | 0·0373 | 0·0488 | 0·0976 | 0·146 | 0·244 |
| log $I_a$ | −0·60 * | +0·21 | 0·36 | 0·41 | 0·65 | 0·77 | 0·94 |
| $ZnCl_2$ (M) | 0·488 | 0·732 | 1·22 | 1·46 | | | |
| log $I_a$ | 1·00 | 0·94 | 0·88 | 0·88 | | | |

* Values deduced from data given in reference 5.

TABLE 4. *Ionisation of* 4 : 4′-*dimethoxydiphenylmethanol* (P) *and its chloride* (Q) *in acetic acid containing both hydrogen chloride and zinc chloride, at* 18° ± 2°.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (i) HCl = 0·0M | | | | | | | |
| $ZnCl_2$ (M) | 0·147 | 0·351 | 0·369 | 0·738 | 1·053 | 1·404 | 1·475 |
| log $I_Q$ | −3·73 | — | −2·76 | −1·80 | — | — | −0·85 |
| log $I_P$ | — | −2·86 | — | — | −1·34 | −0·94 | |
| (ii) HCl = 0·0099M | | | | | | | |
| $ZnCl_2$ (M) | 0·039 | 0·079 | 0·157 | 0·393 | 0·786 | 1·571 | |
| log $I_P$ | −2·08 | −1·79 | −2·22 | −2·69 | −1·89 | −0·93 | |
| (iii) HCl = 0·016M | | | | | | | |
| $ZnCl_2$ (M) | 0·079 | 0·157 | 0·393 | 0·786 | 1·571 | | |
| log $I_P$ | −1·64 | −1·39 | −2·47 | −1·82 | −0·92 | | |
| (iv) HCl = 0·027M | | | | | | | |
| $ZnCl_2$ (M) | 0·072 | 0·144 | 0·361 | 0·452 | 0·722 | 1·445 | |
| log $I_P$ | −1·55 | −1·11 | −0·90 | −1·01 | −1·34 | −0·76 | |
| (v) HCl = 0·054M | | | | | | | |
| $ZnCl_2$ (M) | 0·157 | 0·393 | 0·786 | 1·178 | 1·571 | | |
| log $I_P$ | −1·03 | −0·51 | −0·59 | −0·79 | −0·58 | | |

TABLE 5. *Ionisation of triphenylmethyl chloride* (R) *in acetic acid in the presence of zinc chloride at* 18° ± 2°.

| [$ZnCl_2$] (M) | 0·298 | 0·447 | 0·596 | 0·745 | 0·894 | 1·341 |
|---|---|---|---|---|---|---|
| log $I_R$ | −2·29 | −1·81 | −1·53 | −1·05 | −0·78 | −0·09 |

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*Received, October* 23*rd*, 1957.]

## 390. *The Kinetics of Hydrogen-isotope Exchange Reactions. Part VII.* Aromatic Hydrogen Exchange in the Solvent Systems* $ZnCl_2$–$CH_3{\cdot}CO_2H$ *and* $ZnCl_2$–HCl–$CH_3{\cdot}CO_2H$.

By D. P. N. Satchell.

The rate of the acid catalysed hydrogen-isotope exchange between *p*-deuteroanisole and the solvent systems named in the Title has been measured at 25°. The rate parallels, to a close approximation, the extent of ionisation of indicators such as 4-chloro-2-nitroaniline and *p*-nitrodiphenylamine in these systems. The ionisation process of these compounds is, therefore, considered to involve only hydrogen transfer. The details of the exchange mechanism are discussed.

Very little work has been done on hydrogen-isotope exchange caused by suitable Lewis and Brønsted acids working together, and there exist only three such previous studies which concern the exchange of aromatic hydrogen.[1] The first two [1a,1b] show that the presence of aluminium chloride facilitates the exchange between hydrogen chloride and benzene. The third [1c] demonstrates that the exchange between toluene and dissolved stannic chloride–hydrogen chloride mixtures is of first order in each component. This meagre information, and the fact that the function of such dual-acid systems in promoting hydrogen exchange is likely to be connected with their other catalytic rôles, notably that in the Friedel–Crafts reaction,† encourages further study. The systems $ZnCl_2$–$CH_3{\cdot}CO_2H$ and $ZnCl_2$–HCl–$CH_3{\cdot}CO_2H$ were chosen here, the acetic acid functioning both as a potential Brønsted acid and as the solvent for the other components.

Recent work [2] on aromatic hydrogen exchange, with systems containing only Brønsted acids, has shown that the rate of reaction is governed by the $H_0$ acidity function for the medium. In work with dual-acid catalysts it is, therefore, natural to look for a similar correlation with indicator ionisation. Thus the work has two aspects: the measurement, in the present media, of the ionisation of indicators commonly used in acidity-function studies (preceding paper) and the measurement of the hydrogen-isotope exchange rates between them and some suitable aromatic compound, now described.

*Experimental.—Materials.* *p*-Deuteroanisole,[3] anhydrous acetic acid,[3] anhydrous hydrogen chloride, and stock solutions of the last in the second, were prepared as previously described,[4] as were the stock solutions of zinc chloride.[5]

*Hydrogen-exchange Experiments.*—These were conducted essentially as for sulphuric acid–acetic acid media.[3] The anisole concentration was *ca.* 0·08M and tests showed there to be no loss of it from the reaction mixtures. Good first-order plots were obtained in all cases.

### Discussion and Results

$ZnCl_2$–$CH_3{\cdot}CO_2H$ *Solvent System.*—In pure acetic acid *p*-deuteroanisole undergoes hydrogen exchange negligibly slowly at ordinary temperatures.[3] The addition of zinc chloride to the solvent enhances its acidity,‡ and at salt concentrations above 2M or so, the exchange rate at 25° becomes conveniently measurable. The first-order [2] exchange rate constants, $\lambda$, for zinc chloride concentrations between 1·90 and 3·19M are given in Table 1. Their logarithms, plotted against values of the logarithms of the ionisation ratios for the indicator *p*-nitrodiphenylamine for the same range,‡ yield a straight line of slope 1·14.

* Part VI, *J.*, 1956, 3911. † See following paper. ‡ See preceding paper.

[1] (*a*) Kenner, Polanyi, and Szego, *Nature*, 1935, **135**, 267; (*b*) Klit and Langseth, *Z. phys. Chem.*, 1936, *A*, **176**, 65; (*c*) Comyns, Howald, and Willard, *J. Amer. Chem. Soc.*, 1956, **78**, 3989.

[2] Gold and Satchell, *J.*, 1955, 3609, 3619; Mackor, Smit, and van der Waals, *Trans. Faraday Soc.*, 1957, **53**, 1309.

[3] Satchell, *J.*, 1956, 3911.

[4] Satchell, *J.*, 1958, 1916.

[5] Bethell, Gold, and Satchell, preceding paper.

A similar plot, using the ionisation data for 4-chloro-2-nitroaniline, has a slope of 0·93. It is clear that the rate of aromatic exchange in these solutions is directly related to the extent of ionisation of indicator bases of the type used by Hammett in his studies on acidity. In this, the observed behaviour is exactly analogous to that found in aqueous solution.[2]

TABLE 1. *First-order exchange rate constants, λ, for* p-*deuteroanisole in solutions of zinc chloride in acetic acid at 25°.*

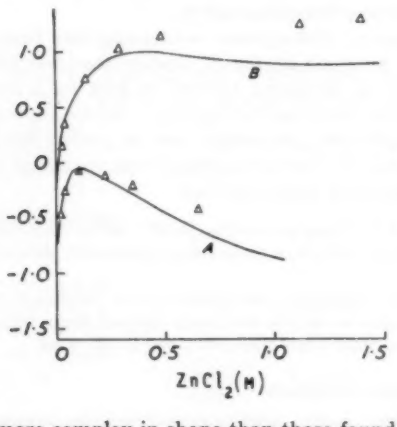
| $ZnCl_2$ (M) | 1·90 | 2·07 | 2·68 | 3·19 |
|---|---|---|---|---|
| $10^7\lambda$ (sec.$^{-1}$) | 3·10 | 4·05 | 8·15 | 16·6 |
| $-\log I$ | 0·78 | 0·69 | 0·40 | 0·14 |

$I$ = Ionisation ratio for *p*-nitrodiphenylamine.

TABLE 2. *First-order exchange rate constants, λ, for* p-*deuteroanisole in acetic acid containing both zinc chloride and hydrogen chloride at 25°.*

| (i) HCl = 0·05M | | | | | | | |
|---|---|---|---|---|---|---|---|
| $ZnCl_2$ (M) | 0·015 | 0·040 | 0·101 | 0·220 | 0·350 | 0·650 | |
| $10^7\lambda$ (sec.$^{-1}$) | 3·24 | 5·81 | 7·90 | 7·22 | 6·04 | 3·71 | |
| (ii) HCl = 0·42M | | | | | | | |
| $ZnCl_2$ (M) | 0·024 | 0·048 | 0·144 | 0·290 | 0·480 | 1·12 | 1·48 |
| $10^7\lambda$ (sec.$^{-1}$) | 13·6 | 21·9 | 57·0 | 105 | 139 | 177 | 201 |

$ZnCl_2$–HCl–$CH_3{\cdot}CO_2H$ *Solvent System.*—In this system the presence of hydrogen chloride enhances the acidity produced by a given amount of zinc chloride, and the plots of log $I$ against zinc chloride concentration, at constant hydrogen chloride concentration,




*Correlation of exchange rates with indicator ionisation in acetic acid containing both hydrogen chloride and zinc chloride.*

$\Delta = 6 + \log\lambda$. $A$ = log $I$ at [HCl] = 0·05M. $B$ = log $I$ at HCl = 0·42M.

are more complex in shape than those found in the presence of zinc chloride alone.* The Figure shows the results of two series of experiments conducted at different constant hydrogen chloride concentrations. In it both log λ and log $I$ for *p*-nitrodiphenylamine in these solutions * are plotted; the exchange rates and the ionisation ratios again follow very similar trends. The parallelism is not exact at high zinc chloride concentrations, but the marked similarity in the shapes and relative dispositions of the ionisation and exchange curves for different hydrogen chloride concentrations is evidence that in this system also the exchange rate and the extent of ionisation of indicators like *p*-nitrodiphenylamine are closely connected.

*Nature of the Ionisation Process in These Media.*—The aromatic hydrogen-isotope exchange in these systems is doubtless acid-catalysed—all the solvent components are acids. Since such hydrogen exchange can, by its very nature, only reflect a Brønsted

* See preceding paper.

acidity, it seems very likely in view of the direct relation which exists between the exchange rates and the extent of the ionisation of basic indicators that the ionisation process, for the indicators concerned, also involves only proton transfer. Free zinc chloride may be present in solution, but direct interaction between it and the indicators can only play a minor rôle in their ionisation. The chemical formulation of the active acidic species is discussed in the preceding paper.

*Mechanism of the Exchange Reaction.*—As has been mentioned, in aqueous solutions of mineral acids the rate of aromatic hydrogen exchange parallels the ionisation of indicator bases in the same way as in the present media. The detailed mechanism in aqueous solution has been discussed previously.[2] We consider it to be represented, in essentials, by the scheme:

$$RD + H^+ \underset{\text{Fast}}{\rightleftharpoons} \underset{\pi_1}{RDH^+} \xrightarrow[\text{Slow}]{} \underset{\pi_2}{RHD^+} \xrightarrow[\text{Fast}]{} RH + D^+$$

in which RD represents a deuterated aromatic molecule, $\pi_1$ and $\pi_2$ are " outer " complexes present in small concentration, and the deuterium content of the system is taken as negligible compared with that of protium.

In acetic acid, where ionic species exist largely as ion-pairs, an anion will presumably be associated with the outer complexes during the slow step, and the solvent acids will be largely undissociated. The analogous kinetic formulation is therefore as follows:

$$RD + HA_i \underset{\text{Fast}}{\rightleftharpoons} \underset{\pi_1}{RDH^+A_i^-} \xrightarrow[\text{Slow}]{} \underset{\pi_2}{RHD^+A_i^-} \xrightarrow[\text{Fast}]{} RH + DA_i$$

If $k$ represents the rate constant of the slow step, $K_a^{RDH^+A_i^-}$ the equilibrium constant of the first step, and X the transition state, then, for a single acid $HA_i$, the Brønsted rate equation is:

$$\text{Rate} = k(RD)(HA_i)/K_a^{RDH^+A_i^-}.f_X \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where parentheses represent activity, and $f$ an activity coefficient. For more than one acid, if $f_X$ and $k$ are assumed to be independent of the particular anion involved, then

$$\text{Rate} = \frac{k(RD)}{f_X} \sum_i (HA_i)/K_a^{RDH^+A_i^-} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The first-order exchange rate constant, $\lambda$, is then

$$\lambda = \frac{kf_{RD}}{f_X} \sum_i (HA_i)/K_a^{RDH^+A_i^-} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The indicators being assumed also to exist largely as ion-pairs in the ionised condition, then the expression for $I$ is [4]

$$I = \sum_i (HA_i)f_B/K_a^{BH^+A_i^-}.f_Y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where B is a given indicator, Y the ion-pair $BH^+A_i^-$, and $K_a^{BH^+A_i^-}$ the ionisation constant for ion-pair formation. If the values of $f_Y$ for different ion-pairs be taken as equal, then

$$I = \frac{f_B}{f_Y} \sum_i (HA_i)/K_a^{BH^+A_i^-} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

In equations (3) and (5) the activity coefficient ratios refer to species of similar structure and might be expected to vary in roughly the same way with medium composition. The equilibrium constants $K_a^{BH^+A_i^-}$ and $K_a^{RDH^+A_i^-}$ are for ion-pair formation between a given acid, $HA_i$, and the bases B and RD. If their ratio for different acids may, as a first approximation, be taken to be constant, then $\lambda$ would be expected to follow the trend of $I$, as is found experimentally. The assumption concerning the constancy of the equilibrium constant ratio is only necessary if more than one acid is active. This is very probably the case in the solutions containing both hydrogen chloride and zinc chloride,

and therefore it is not very surprising that in these solutions the correlation is not exact. As has been previously pointed out,[4] it is probably the fact that such ratios are not constant which is the major cause for the lack of exact parallelism observed for the ionisation of different indicators under such conditions. However, it is clear that the type of mechanism suggested for aqueous exchange remains satisfactory in acetic acid.

The only likely alternative mechanism is that depicted in the following scheme, in which there is a rate-determining attack by the acid species, *i.e.*, $k_1 \ll k_{-1}$ or $k_2$.

$$HA + RD \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RDH^+A^- \xrightarrow{k_2} RH + DA$$

If it is assumed that the activity coefficients of the transition states of each step are the same, and of value $f_Z$, then

$$\text{Rate} = [k_1k_2/(k_{-1} + k_2)](RD)(HA)/f_Z \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

If there is more than one acid active, and if the ratio $k_2/(k_{-1} + k_2)$ $(= \phi)$, and also $f_Z$, be considered independent of the acid involved, then

$$\text{Rate} = (RD)\phi[\sum_i k_{1i}(HA_i)]/f_Z \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Or

$$\lambda = \phi f_{RD}[\sum_i k_{1i}(HA_i)]/f_Z \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

For $\lambda$ to parallel $I$ on this basis, the ratio $f_{RD}/f_Z$ must show similar variations to the ratio $f_B/f_Y$, and the product $k_{1i} \cdot K_a^{BH^+A_i^-}$ must be approximately constant for different acids. On the whole these conditions seem rather less likely to be satisfied than those for the previous mechanism, especially since the proton of the attacking acid may be solvated, and then Y and Z will not represent similar molecular aggregates. However, it is obviously not possible to make a definite decision at present.

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## 391. *Aromatic Alkylation. Part II.*[1] *Diarylmethylation Reactions in the Solvent Systems* $ZnCl_2$–$CH_3{\cdot}CO_2H$ *and* $ZnCl_2$–$HCl$–$CH_3{\cdot}CO_2H$.

By D. BETHELL and V. GOLD.

The diarylmethylation of anisole in acetic acid is catalysed by zinc chloride and by mixtures of zinc chloride and hydrogen chloride in a manner which parallels the effect of these substances on the ionisation ratios of an indicator of similar structure to the aralkylating reagent. The reagent is introduced as diarylmethyl chloride or acetate but, under the experimental conditions, it is always present predominantly in the form of the acetate. The results show that the main function of zinc chloride in the reaction is the generation of Brønsted acidity in the solution by virtue of its interaction with the co-catalysts hydrogen chloride and acetic acid, and the concomitant production of carbonium ions from the reagent. The substitution step proper is again the bimolecular reaction between diarylcarbonium ions and anisole.

WITH sulphuric acid as catalyst, aromatic aralkylation by diphenylmethanol XOH (or its acetate) involves a bimolecular reaction between a rapidly formed carbonium ion and the other reagent (ArH).[1] It seemed of interest to study the same reaction in the same solvent with a Friedel–Crafts catalyst of the Lewis acid metal halide type so as to afford a comparison of the mechanisms. Zinc chloride is a comparatively mild catalyst of this type and it was selected because of the known absence of complication by solvolysis,[2]

[1] Part I, Bethell and Gold, *J.*, 1958, 1905.
[2] Davidson and Chappell, *J. Amer. Chem. Soc.*, 1939, **61**, 2164.

whereas the more typical catalyst, aluminium chloride, is rapidly attacked by acetic acid.[3]

The plan followed that of the study of sulphuric acid catalysis [1] in that measurements of reaction rates were paralleled by indicator measurements [4] on related diarylmethyl compounds.

In the earlier experiments the aralkylating agent was introduced in the form of the chloride, as is usual in halide-catalysed Friedel–Crafts reactions, but during the course of the investigation it became clear that a solvolytic pre-equilibrium with formation of diarylmethyl acetate is rapidly established and that the simultaneously formed hydrogen chloride functions as a co-catalyst in the reaction.

## Experimental

Solutions of zinc chloride and hydrogen chloride were prepared as before.[4] Whenever possible, blocks of kinetic experiments and their corresponding indicator measurements were made with a single stock solution.

Diarylmethanols and their acetates were the specimens previously prepared.[1] Diarylmethyl chlorides were prepared from the corresponding alcohols by passing hydrogen chloride through the ethereal solution and removing the water formed ($CaCl_2$). Diphenylmethyl chloride was twice distilled under reduced pressure (b. p. 156—158°/10 mm.; m. p. 19°); the 4-methoxy-compound was recrystallised from ether or light petroleum.

The reactions studied kinetically were also carried out on a preparative scale and the pure products isolated in yield exceeding 92%.

Kinetic runs were followed spectrophotometrically. A 5 ml. sample of the reaction mixture was quenched by ten-fold dilution with absolute or (in the case of higher catalyst concentrations) slightly aqueous ethanol. Absorption intensities of the diluted samples were related to the progress of a reaction by reference to a previously constructed calibration curve, as the spectrum at the completion of a reaction was not a simple superposition of the separate spectra of reagents and products. Synthetic mixtures of reagents, catalyst, and products in acetic acid–ethanol (10 : 90 by vol.) were therefore prepared to simulate diluted samples at the various stages of

Table 1. *Alkylation of anisole by diphenylmethyl chloride or diphenylmethyl acetate.*

$[XCl]_{initial}$ or $[XOAc]_{initial}$ = 0·027M. No addition of hydrogen chloride.

| Series * | $[ZnCl_2]$ | $[Anisole]_{initial}$ | $10^5k_2$ (l. mole$^{-1}$ sec.$^{-1}$): for chloride | for acetate | Series | $[ZnCl_2]$ | $[Anisole]_{initial}$ | $10^5k_2$ (l. mole$^{-1}$ sec.$^{-1}$): for chloride | for acetate |
|---|---|---|---|---|---|---|---|---|---|
| A | 0·046 | 0·463 | 4·13 | — | A | 0·461 | 0·463 | 25·8 | — |
| B | 0·070 | ,, | 6·67 | — | A | 0·553 | ,, | 16·8 | — |
| A | 0·092 | ,, | 8·90 | — | A | ,, | 0·926 | 20·3 | — |
| B | 0·176 | ,, | 18·3 | — | B | 0·702 | 0·463 | 13·8 | 4·21 |
| A | 0·184 | ,, | 22·1 | — | A | 0·922 | ,, | 27·8 | — |
| A | ,, | ,, | 22·9 | — | B | 1·053 | ,, | 31·4 | 17·1 |
| B | 0·351 | ,, | 26·4 | 0·354 | A | 1·199 | ,, | 54·5 | — |
| A | 0·369 | ,, | 33·0 | — | B | 1·404 | ,, | 72·5 | 49·7 |
| A | ,, | 0·926 | 34·1 | — | A | 1·475 | ,, | 90·7 | — |

* Series A and B relate to different batches of solvent.

Table 2. *Alkylation of anisole by 4-methoxydiphenylmethyl chloride.*

$[XCl]_{initial}$ = 0·010M. $[Anisole]_{initial}$ = 0·213M. No addition of hydrogen chloride. $k_2$ in l. mole$^{-1}$ sec.$^{-1}$.

| $[ZnCl_2]$ (M) ... | 0·011 | 0·022 | 0·054 | 0·108 | 0·162 | 0·216 | 0·323 | 0·398 | 0·431 | 0·597 | 0·796 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $10^5k_2$ ..... | 13·6 | 26·1 | 75·3 | 103·0 | 50·7 | 14·0 | 11·1 | 19·0 | 22·0 | 57·5 | 120·7 |

the reaction. The observed " infinity " readings agreed satisfactorily (within 5%) with the " synthetic " values expected from the initial concentrations of reagents. In all cases the observed course of the reactions was made to be of first order by employing a large excess of

[3] Funk and Schormüller, *Z. anorg. Chem.*, 1931, **199**, 93.
[4] Bethell, Gold, and Satchell, *J.*, 1958, 1918.

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the aromatic compound ArH, and rate constants were evaluated graphically by plotting log $(100 - x)$ against $t$, where $x$ is the percentage of unchanged alkylating agent remaining in solution after a time $t$. Second-order rate constants, $k_2$, calculated as before,[1] indicated that the reaction is of first order with respect to ArH.

All rate constants relate to a temperature of 25°.

## Discussion

The main series of experiments relates to the aralkylation of anisole by diphenylmethyl chloride and its 4-methoxy-derivative under the influence of added zinc chloride. In each case the rate exhibits a rather characteristic dependence on the catalyst concentration (Figs. 1 and 2), unlike that found for the ionisation ratio of 4 : 4′-dimethoxydiphenylmethyl chloride under the influence of added zinc chloride, but without addition of hydrogen

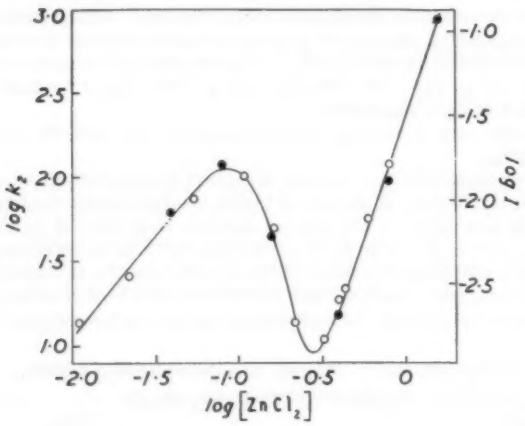


Fig. 1. *Methoxydiphenylmethylation rates and ionisation ratios.*

[HCl] or [RCl] = 0·01M.

○, Velocity constants.
●, Ionisation ratios.

chloride.[4] On the other hand, the curves resemble the behaviour of the indicator in the presence of both zinc chloride and hydrogen chloride.[4] If the mechanism of aralkylation under the influence of zinc chloride is the same as for the case of catalysis by sulphuric acid,[1] then it would be expected that the rates should again parallel indicator ionisation ratios as was found in the latter case. A closer examination of the results of the present paper shows that this parallelism does indeed also obtain for the catalysis of zinc chloride.

The reason for the apparent lack of agreement lies in the setting up of the equilibrium

$$RCl + AcOH \rightleftharpoons R{\cdot}OAc + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

In absence of zinc chloride and hydrogen chloride, esterification of the organic chloride is slow, and the ultraviolet absorption spectrum of a solution of diphenylmethyl chloride in acetic acid differs significantly from that of one of diphenylmethyl acetate in the same solvent. However, upon addition of zinc chloride the absorption spectrum of the organic chloride changes rapidly and becomes identical with that of the acetate (Fig. 3). This indicates that under the conditions of these experiments diphenylmethyl chloride is quantitatively converted into the acetate. (The experiments do not disprove the possibility that some of the acetate is hydrolysed by traces of water in the solvent, but the general character of the results renders this unlikely.) Indicator measurements were carried out on very dilute solutions of the indicator, and consequently the solvolysis does not result in any appreciable concentration of hydrogen chloride in the solution. The

organic chloride concentration was considerably higher in the kinetic experiments, and consequently the media for indicator and for kinetic experiments differed in that the latter contained an appreciable concentration of hydrogen chloride, whereas the former did not. It is now apparent that the rate constants should be related to indicator measurements at a hydrogen chloride concentration equivalent to that of diarylmethyl chloride in the kinetic experiments. This is shown in Fig. 1, where the circles represent velocity constants and the dots ionisation ratios (the latter in the presence of 0·01M added hydrogen chloride); both sets of data fall on the same curve. Similarly, the half-moons in the upper curve of Fig. 2 denote velocity constants, and the crosses ionisation ratios, in the presence of the appropriate concentration of hydrogen chloride. The circles in the lower curve of Fig. 2 represent ionisation ratios for the indicator (in very low concentration), without addition of hydrogen chloride. It is evident that they are not simply related to the data in the upper curve. On the other hand, the dots in the diagram represent reaction velocities when the

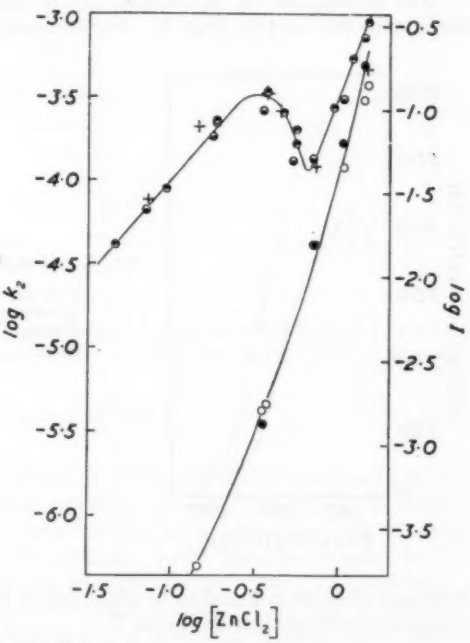


FIG. 2. *Diphenylmethylation rates and ionisation ratios.*

Upper curve: ◓ Series A } ◒ Series B } log $k_2$; [XCl] = 0·027M.
+ log $I$; [HCl] = 0·027M.
Lower curve: ● log $k_2$; [XOAc] = 0·027M.
○ log $I$; [HCl] = 0.

reagent is introduced as acetate (so that no hydrogen chloride is set free by solvolysis). These reaction velocities are seen to fall on the lower curve. The indicator data used in both sets of comparisons (Figs. 1 and 2) relate to 4 : 4′-dimethoxydiphenylmethyl chloride (or the alcohol).[4] The agreement obtained is very good for the results in Fig. 1; for those in Fig. 2 the rate constants increase slightly relative to the ionisation ratios. The reason for this slight discrepancy is not clear, but not entirely unexpected in the light of the more general considerations applying to this solvent system.[4] The good agreement in the case of the results with 4-methoxydiphenylmethyl chloride indicates that ion-association phenomena must be very similar for the 4-methoxydiphenylcarbonium ion and the 4 : 4′-dimethoxydiphenylcarbonium ion formed from the indicator. This agreement also indicates that the forward reaction of equilibrium (1) must be virtually complete, even when some hydrogen chloride is present in solution, and extends the result derived from the study of absorption spectra in the presence of added zinc chloride alone. (In all cases

studied the actual concentration of hydrogen chloride in solution is considered to be very low, owing to the interaction of hydrogen chloride and zinc chloride.)

TABLE 3. *Effect of addition of hydrogen chloride on the rate of alkylation of anisole by diphenylmethyl chloride or diphenylmethyl acetate.*

$[XCl]_{initial}$ or $[XOAc]_{initial} = 0{\cdot}027$M. $[Anisole]_{initial} = 0{\cdot}463$M. $k_2$ in l. mole$^{-1}$ sec.$^{-1}$.

| Reagent | $[ZnCl_2]$ (M) | $[HCl]_{added}$ | $[HCl]_{added}$ + $[XCl]_{initial}$ | $10^5k_2$ | Reagent | $[ZnCl_2]$ (M) | $[HCl]_{added}$ | $[HCl]_{added}$ + $[XCl]_{initial}$ | $10^5k_2$ |
|---|---|---|---|---|---|---|---|---|---|
| XCl | 0·070 | — | 0·027 | 6·67 | XCl | 0·351 | 0·022 | 0·049 | 76·9 |
| XOAc | 0·070 | — | — | Very slow | XOAc | 0·351 | 0·022 | 0·022 | 13·8 |
| XOAc | 0·070 | 0·027 | 0·027 | 6·80 | XCl | 1·053 | — | 0·027 | 31·4 |
| XCl | 0·351 | — | 0·027 | 26·4 | XOAc | 1·053 | 0·027 | 0·027 | 32·8 |

The importance of equilibrium (1) is supported by the kinetic experiments with diphenylmethyl acetate (Fig. 2). Furthermore, a mixture of diphenylmethyl acetate and

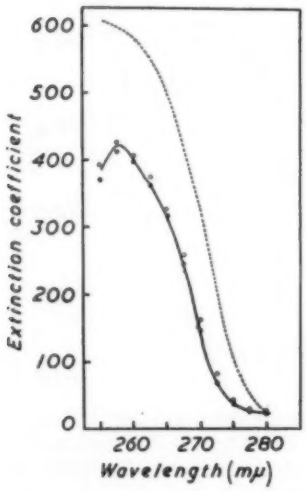


FIG. 3. *Absorption spectra of diphenylmethyl chloride and acetate.*

Full curve: $Ph_2CH{\cdot}OAc$ in AcOH.
Broken curve: $Ph_2CHCl$ in AcOH.
Circles: ,, ,, + 0·316M-$ZnCl_2$.
Dots: ,, ,, + 0·702M-$ZnCl_2$.

hydrogen chloride is found to be alkylated at the same rate as the corresponding solution of diphenylmethyl chloride (Table 3).

By an argument analogous to that of Part I, the results indicate that the rate of reaction is proportional to the concentration of carbonium ion formed. The function of the catalyst is explained by the high proton activity of the solutions and is analogous to the catalysis by sulphuric acid. It is essentially the acid cleavage of an ester to produce the active carbonium ions

$$Ph_2CH{\cdot}OAc + H^+ \rightleftharpoons Ph_2\overset{+}{C}H + AcOH \quad . \quad . \quad . \quad . \quad . \quad (2)$$

A consideration of the results along with those of Part I permits the further conclusion that no additional rôle (such as association with anisole) is to be assigned to zinc chloride in the mechanism of the reaction. In view of the esterification and solvolysis equilibria, the un-ionised form of 4 : 4′-dimethoxydiphenylmethanol in sulphuric acid–acetic acid (Part I) will be the same as the un-ionised form of the chloride or acetate. Consequently—leaving aside ion-association phenomena—*all* the indicator measurements relate to the formation of carbonium ions from the same system of un-ionised indicator. Similarly, the

reagent diphenylmethanol will be in the same form as the reagent introduced as diphenylmethyl chloride or acetate, provided that the concentration of alcohol remains unimportant also at the higher concentration. Consequently, if we are justified in writing

$$\log \frac{[\mathrm{XOH}]_{\text{stoich.}}}{[\mathrm{X}^+]} = \log \frac{[\mathrm{ROH}]_{\text{stoich.}} - [\mathrm{R}^+]}{[\mathrm{R}^+]} + \text{const.} \quad . \quad . \quad . \quad (3)$$

it follows that solutions which cause the same conversion of the indicator into carbonium ions will produce the same ionisation ratio for the aralkylating reagent whether it is introduced as alcohol, chloride, or acetate. If zinc chloride has no function beyond producing the acid system which induces the ionisation of the reagent, the coefficient $k$ in the rate equation (Part I, equation 8)

$$v = k[\mathrm{X}^+][\mathrm{ArH}]\frac{f_{\mathrm{X}^+}f_{\mathrm{ArH}}}{f_{\ddagger}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

should have the same value for diphenylmethylations catalysed by zinc chloride–hydrogen chloride or by sulphuric acid. It follows from equations (3) and (4) that a graph of log $k$ against log $I$ should include all points on the same straight line of unit slope. On the other hand, an additional catalytic function of zinc chloride would then be revealed by the points relating to zinc chloride lying *above* the line through the points for catalysis by sulphuric acid. The correctness of the first alternative is indicated in Fig. 4, in which none of the points diverges from the best straight line of *unit slope* by more than a factor of 2. The agreement is remarkable, since the measurements apply to high concentrations of different catalysts, such as might be expected to cause a noticeable medium effect, and to different concentrations of anisole. It also points to the relative unimportance of the chemical nature of the anion associated with the reagent carbonium ion. The result also accords with our observation that zinc chloride does not affect the ultraviolet spectrum of anisole, and therefore presumably does not interact with it chemically.

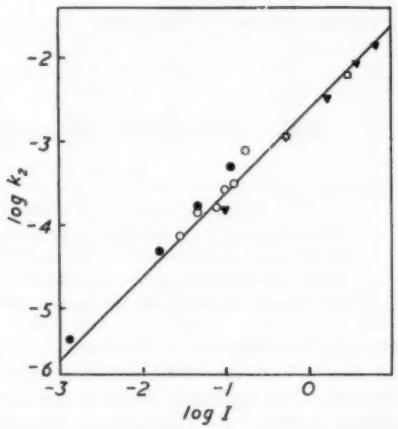


FIG. 4. *Correlation of diphenylmethylation rates of anisole with indicator ionisation ratios for different catalysts and reagents.*

▼, $H_2SO_4$–$Ph_2CH{\cdot}OH$.
□, $H_2SO_4$–$Ph_2CH{\cdot}OAc$.
○, $ZnCl_2$–$Ph_2CHCl$.
●, $ZnCl_2$–$Ph_2CH{\cdot}OAc$.

It is known from other work,[5] particularly in the field of so-called " cationic polymerisation ", that at least some catalysts of the Lewis-acid type are ineffective (in the gas-phase or in non-polar media) unless a co-catalyst is present. Traces of water can fill this rôle and, for this reason, an exact study of the phenomenon in non-polar media is experimentally

[5] Articles in Plesch (ed.), " Cationic Polymerisation and Related Complexes," Heffer, Cambridge, 1953; Burnett, " Mechanism of Polymer Reactions," Interscience Publishers, London and New York, 1954, Chap. XI; Ipatieff, Pines, and Schmerling, *J. Org. Chem.*, 1940, **5**, 253; Toussaint and Hennion, *J. Amer. Chem. Soc.*, 1940, **62**, 1145.

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difficult. The present study and the related work on deuterium exchange in acetic acid [6] demonstrate the operation of co-catalysis in greater detail. In the terminology employed in this field, zinc chloride would be described as the catalyst, and acetic acid and hydrogen chloride as co-catalysts. Our work also shows that co-catalysis, in at least one reaction of the Friedel–Crafts type, is a manifestation of catalysis by a Brønsted acid. It does not follow that co-catalysis by Brønsted acids need be met in all reactions for which zinc chloride is a catalyst.[7]

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, October 23rd*, 1957.]

[6] Satchell, preceding paper.
[7] Bell and Skinner, *J.*, 1952, 2955.

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## 392. *The Dipole Moments of Some Cyclic Carbonates.*

By R. KEMPA and W. H. LEE.

The dipole moments and dielectric constants of ethylene carbonate and monochloro-, 1 : 2-dichloro-, methyl-, and chloromethyl-ethylene carbonate have been determined. The possibilities of intermolecular association in these compounds, and the effects of chlorine- and methyl-substitution on the dipole moment of the parent carbonate, are considered.

DURING an investigation of the solvent properties of cyclic esters of carbonic acid, it was found that anhydrous ferric, mercuric, and zinc chlorides were readily soluble in ethylene carbonate. The solutions show a considerable electrical conductivity, indicating that ionisation occurs. By comparison, the alkali-metal chlorides are practically insoluble in ethylene carbonate.

Anomalous properties of cyclic carbonates have been reported. Newman and Addor [1] noted the decrease in boiling-point of ethylene carbonate upon substitution of chlorine for hydrogen. Hales, Jones, and Kynaston,[2] whilst investigating the infrared absorption spectra of cyclic carbonates, observed two absorption peaks in the carbonyl region for monochloro- and 1 : 2-dichloro-ethylene carbonate. An analogous phenomenon, reported for halogenated esters of acetic acid, was ascribed to intermolecular association,[3] as the doublet was not observed in the case of methyl- and chloromethyl-ethylene carbonate, however, Hales, Jones, and Kynaston [2] considered rotational isomerism to be the more likely explanation of their observed effect.

Values of dipole moments of ethylene carbonate and some other cyclic carbonates have been reported;[4,5] all these compounds possess large dipole moments. Longster and Walker [6] investigated the effect of permanent dipoles on the cohesive energy and solvent action towards high polymers of highly polar substances, and in this context pointed out the high boiling-points and cohesive energies of cyclic, as compared with open-chain, carbonates.

The ability to dissolve electrolytes, with formation of electrically-conducting solutions, depends largely upon the dielectric constant of the solvent and this, in turn, partly upon the dipole moment of the solvent molecule. We have determined the dipole moments and dielectric constants of ethylene carbonate and monochloro-, 1 : 2-dichloro-, methyl-, and chloromethyl-ethylene carbonate, and drawn conclusions regarding the possibilities of intermolecular association in the liquids.

[1] Newman and Addor, *J. Amer. Chem. Soc.*, 1953, **75**, 1263.
[2] Hales, Jones, and Kynaston, *J.*, 1957, 618.
[3] McBee and Christman, *J. Amer. Chem. Soc.*, 1955, **77**, 755.
[4] Arbuzov and Shavsha, *Doklady Akad. Nauk S.S.S.R.*, 1949, **68**, 1045.
[5] *Idem*, *Chem. Abs.*, 1950, **44**, 886.
[6] Longster and Walker, *Trans. Faraday Soc.*, 1953, **49**, 228.

## Experimental

*Materials.*—Ethylene carbonate was fractionally distilled at reduced pressure, and then fractionally crystallised from dry ether. The purified material had m. p. 36·2°, $n_D^{40}$ 1·4199.

Samples of monochloro-, 1 : 2-dichloro-, methyl-, and chloromethyl-ethylene carbonate, prepared as in ref. 7, supplied by Dr. J. Idris Jones. These were redistilled in nitrogen at reduced pressure. Their physical properties are given in the Tables.

The benzene for dipole-moment measurements was prepared from " AnalaR " material by Le Fèvre's method; [8] a comparison sample, purified by Rybicka and Wynne-Jones's procedure,[9] showed no difference in physical properties.

Table 1. *Properties of cyclic carbonates.*

| Substance | $n_D$ | $d_4^{25}$ | $R_D$ | ε *† | $10^{18}\mu$ (e.s.u.) | B. p. |
|---|---|---|---|---|---|---|
| Ethylene carbonate * ..... | 1·4199 | 1·3208 | 16·93 | 89·6 | 4·87 | 238° |
| Methylethylene carbonate ..... | 1·4212 | 1·2065 | 21·46 | 61·7 | 4·94 | 232 |
| Monochloroethylene carbonate ... | 1·4603 | 1·5198 | 22·09 | 62·0 | 3·99 | 212 |
| 1 : 2-Dichloroethylene carbonate... | 1·4615 | 1·5830 | 27·22 | 31·8 | 3·44 | 178 |
| Chloromethylethylene carbonate... | 1·4680 | 1·4403 | 26·35 | 97·5 | 4·68 | 252 |

* Measurements at 40°.

† The results are the mean of three series of determinations. The experimental error is estimated as ± 0·3%.

Table 2. *Total polarisations and dipole moments in benzene.*

Ethylene carbonate

| $x$ | $d_4^{25}$ | ε | $_TP$ | $x$ | $d_4^{25}$ | ε | $_TP$ |
|---|---|---|---|---|---|---|---|
| 0·0 | 0·87366 | 2·2725 | — | 0·0058225 | 0·87584 | 2·4696 | 493·4 |
| 0·0036502 | 0·87496 | 2·3955 | 499·9 | 0·0079409 | 0·87662 | 2·5430 | 488·4 |
| 0·0043616 | 0·87533 | 2·4198 | 497·6 | | | | |

$P_0 = 510·2$; $_DP = 17·8$; $\mu = 4·87 \times 10^{-18}$ e.s.u.

Methylethylene carbonate

| $x$ | $d_4^{25}$ | ε | $_TP$ | $x$ | $d_4^{25}$ | ε | $_TP$ |
|---|---|---|---|---|---|---|---|
| 0·0032595 | 0·87480 | 2·3844 | 515·8 | 0·010327 | 0·87714 | 2·6223 | 484·2 |
| 0·0056013 | 0·87566 | 2·4633 | 502·8 | 0·014818 | 0·87860 | 2·7639 | 461·2 |

$P_0 = 529·0$; $_DP = 23·0$; $\mu = 4·94 \times 10^{-18}$ e.s.u.

Monochloroethylene carbonate

| $x$ | $d_4^{25}$ | ε | $_TP$ | $x$ | $d_4^{25}$ | ε | $_TP$ |
|---|---|---|---|---|---|---|---|
| 0·0034450 | 0·87575 | 2·3503 | 349·1 | 0·0073910 | 0·87807 | 2·4406 | 344·9 |
| 0·0039360 | 0·87613 | 2·3615 | 347·9 | 0·011994 | 0·88078 | 2·5472 | 339·5 |

$P_0 = 352·6$; $_DP = 23·2$; $\mu = 3·99 \times 10^{-18}$ e.s.u.

1 : 2-Dichloroethylene carbonate

| $x$ | $d_4^{25}$ | ε | $_TP$ | $x$ | $d_4^{25}$ | ε | $_TP$ |
|---|---|---|---|---|---|---|---|
| 0·0032137 | 0·87622 | 2·3269 | 273·4 | 0·0085933 | 0·88036 | 2·4194 | 272·7 |
| 0·0053052 | 0·87784 | 2·3623 | 273·2 | 0·012337 | 0·88320 | 2·4858 | 272·1 |

$P_0 = 274·0$; $_DP = 28·6$; $\mu = 3·44 \times 10^{-18}$ e.s.u.

Chloromethylethylene carbonate

| $x$ | $d_4^{25}$ | ε | $_TP$ | $x$ | $d_4^{25}$ | ε | $_TP$ |
|---|---|---|---|---|---|---|---|
| 0·0042304 | 0·87637 | 2·4041 | 470·6 | 0·0082567 | 0·87877 | 2·5302 | 460·4 |
| 0·0054554 | 0·87705 | 2·4428 | 468·7 | 0·010219 | 0·87998 | 2·5913 | 454·6 |

$P_0 = 481·8$; $_DP = 27·7$; $\mu = 4·68 \times 10^{-18}$ e.s.u.

*Dipole Moments.*—Determinations were made in benzene solutions by a resonance method with the apparatus described by Few, Smith, and Witten.[10] The crystal-controlled oscillator frequency was $10^6$ c./sec., and the capacitance was measured by a Sullivan precision air condenser. The cell was of an all-glass type, similar to that described by Le Fèvre, and had a capacitance of 65 μμF per dielectric-constant unit.

Densities were determined by a modified Sprengel–Ostwald pyknometer of *ca.* 20 c.c. capacity, and refractive indices by an Abbé refractometer.

[7] " Chemistry Research," 1953. Department of Scientific and Industrial Research, pp. 37—38; 1954, pp. 35—36.
[8] Le Fèvre, " Dipole Moments," Methuen's Monograph, London, 1948.
[9] Rybicka and Wynne-Jones, *J.*, 1950, 3671.
[10] Few, Smith, and Witten, *Trans. Faraday Soc.*, 1952, **48**, 211.

*Dielectric Constants.*—The above resonance apparatus was used, but with a Hartley–Barrett type of conductivity cell. The distance between the two plane-parallel bright platinum electrodes was adequate to prevent errors due to the fringing effect of capacitance between the adjacent mercury-filled lead-in tubes. This effect was reduced further by always using the same volume of liquid in the cell.

Methanol–water mixtures of known dielectric constant, as determined by Albright and Gosting,[11] were used to calibrate the cell. The measurements were made at 40°, so that it was necessary to calculate dielectric constants at 40° for the calibrating solutions by linear interpolation between 35° and 45°.

*Results.*—The results are summarised in Tables 1 and 2. Molar refractions, $R_D$, were derived from densities and refractive indices of the pure compounds at 25°, except for ethylene carbonate (40°). $P_0$ was obtained by extrapolation to zero concentration of values of ${}_TP$, the total polarisation at mole fraction $x$. Dipole moments were calculated from $\mu = 0{\cdot}01275\sqrt{[(P_0 - {}_DP)T]}$ where the distortion polarisation, ${}_DP$, is given by ${}_DP = P_{atom} + P_{electron} = 1{\cdot}05R_D$.

## Discussion

The value obtained for the dipole moment, $\mu$, of ethylene carbonate in benzene agrees well with those of Arbuzov and Shavsha [4] (4·80 D) and Longster and Walker [6] (4·60 D). The substitution of hydrogen by a methyl group increases $\mu$ by 0·07 D; Arbuzov and Shavsha found the same increase between 1 : 3-propylene carbonate ($\mu = 5{\cdot}21$ D) and 1 : 3-butylene carbonate ($\mu = 5{\cdot}28$ D). For 2 : 3-butylene carbonate an even higher dipole moment ($\mu = 5{\cdot}26$ D) was found.[6] This increase of dipole moment on introduction of methyl groups as substituents was generally observed by Baker,[12] and has been extensively investigated. The effect, as seen in Tables 1 and 2, is only slightly reduced by substitution by a monohalogenated methyl group.

Chlorine atoms, directly attached to the ethylene carbonate ring, decrease $\mu$; this is not surprising, for the group moment of the C–Cl linkage is in opposition to the resultant moment of the carbonate group. The same conclusion can be reached for vinylene carbonate. Slayton, Simmons, and Goldstein [13] found $\mu = 4{\cdot}51$ D, less than that of ethylene carbonate. The double bond is localised, the characteristic C=O absorption band being unchanged as compared with that of other cyclic carbonates.[2] If the double bond were delocalised, however, a decrease in absorption within this band would be expected. The accumulation of negative charge due to the $\pi$-bond causes a moment opposing that of the carbonate group.

The forces between the molecules of a liquid are usually classified as orientation forces, dispersion forces, and inductive forces. The first are particularly important in the case of highly polar molecules, and the last are very small. The dielectric constant of a medium can be regarded as a semi-quantitative resultant of these forces.

The progressive reduction in b. p. and dielectric constant, with replacement of hydrogen by chlorine in ethylene carbonate, reflects mainly the decreasing dipole moment. The orientation forces are presumably weaker, in vinylene carbonate, for here a "normal" b. p. (162°) and high dipole moment are found.

The change from a methylene carbonate to the monochloro-derivative leads to the expected decrease in dipole moment, but there is a small increase in b. p. and a large increase in dielectric constant. It is thought that intermolecular hydrogen bonding may assist dipole interaction in the last case.

We thank the German Academic Exchange Service for the award of a grant (to R. K.), and Dr. J. Idris Jones, Chemical Research Laboratory, Teddington, for helpful discussion, and for supplying samples of cyclic carbonates.

Battersea College of Technology,
London, S.W.11. [*Received, July 9th*, 1957.]

[11] Albright and Gosting, *J. Amer. Chem. Soc.*, 1946, **68**, 1061.
[12] Baker, *J.*, 1939, 1152.
[13] Slayton, Simmons, and Goldstein, *J. Chem. Phys.*, 1954, **22**, 1678.

## 393. *The Stereochemistry of Molecules containing the* N=C=N *Group: the Structure of the Monomethiodide of Bis-*p*-dimethylaminophenylcarbodi-imide.*

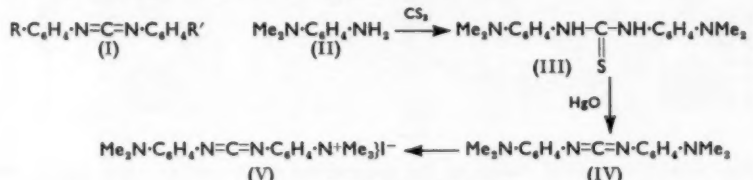
By J. J. Daly and P. J. Wheatley.

Cell dimensions and space-groups of three carbodi-imides have been determined and the structure of one of them, the monomethiodide of bis-*p*-dimethylaminophenylcarbodi-imide (V) established. This substance is orthorhombic $Pca2_1$ with $a = 40{\cdot}50$ Å, $b = 5{\cdot}67$ Å, $c = 8{\cdot}24$ Å. A two-dimensional analysis based on $hk0$ intensities shows that the shape of the molecule conforms to that predicted by classical stereochemistry. The central C–N=C=N–C chain is bent, in contrast to the linear C=C=N–C chain found in some vinylideneamines. The line containing the N=C=N system does not lie in the plane of either of the benzene rings. This lack of co-planarity is similar to that found in *cis*-azobenzene, and suggests that there is little resonance across the =N– system.

A carbodi-imide [1] of the type R·N=C=N·R should exist in enantiomorphous forms if the bonds at the nitrogen atoms are not collinear.[2] Attempts have been made to resolve these compounds without success.[3] It has recently been shown [4,5] that the C=C=N–C chain can be linear, and it therefore seemed possible, notwithstanding reports of a finite dipole moment by Bergmann and Scheutz,[6] that failure to resolve carbodi-imides might be due to the linearity of the C–N=C=N–C chain. However, the *X*-ray examination of a carbodi-imide described below shows that the chain is bent.

### Experimental

The carbodi-imides examined were all of the type (I). Samples of di-*p*-tolylcarbodi-imide (I; R = R′ = Me) and bis-*p*-dimethylaminophenylcarbodi-imide (IV) were kindly supplied by Sir Alexander Todd. Further quantities of the latter were made by condensation of *p*-dimethylaminoaniline (II) with carbon disulphide in benzene to give the thiourea (III), followed by removal of hydrogen sulphide with yellow mercuric oxide.[7]




(All substituents *para*)

The carbodi-imide (IV) gave the same *X*-ray diagram and had the same melting point as that supplied by Professor Todd. The monomethiodide (V) was prepared by the action of methyl iodide on the base (IV) in benzene [8] and was recrystallised from acetone. The melting point was 165°, as given by Zetzsche and Baum.[8]

The cell dimensions and space-groups of the three carbodi-imides examined are:

| R (in I) | R′ (in I) | $a$ (Å) | $b$ (Å) | $c$ (Å) | Space-group | $z$ | $d_{obs.}$ (g./c.c.) | $d_{calc.}$ (g./c.c.) |
|---|---|---|---|---|---|---|---|---|
| Me | Me | 11·30 | 14·78 | 7·70 | $P2_12_12_1$ | 4 | — | — |
| $NMe_2$ | $NMe_2$ | 7·46 | 33·32 | 6·29 | $P2_12_12_1$ | 4 | 1·16 | 1·19 |
| $NMe_2$ | $(NMe_3)^+I^-$ | 40·50 | 5·67 | 8·24 | $Pca2_1$ | 4 | 1·46 | 1·48 |

[1] Khorana, *Chem. Rev.*, 1953, **2**, 145.
[2] Sidgwick, "The Organic Chemistry of Nitrogen," New edn., revised by Taylor and Baker, Oxford Univ. Press, 1942.
[3] Rolls and Adams, *J. Amer. Chem. Soc.*, 1932, **54**, 2494.
[4] Wheatley, *Acta Cryst.*, 1954, **7**, 68.
[5] Bullough and Wheatley, *ibid.*, 1957, **10**, 233.
[6] Bergmann and Scheutz, *Z. phys. Chem.*, 1932, *B*, **19**, 389.
[7] Zetzsche and Nerger, *Ber.*, 1940, **73**, 467.
[8] Zetzsche and Baum, *Ber.*, 1942, **75**, 100.

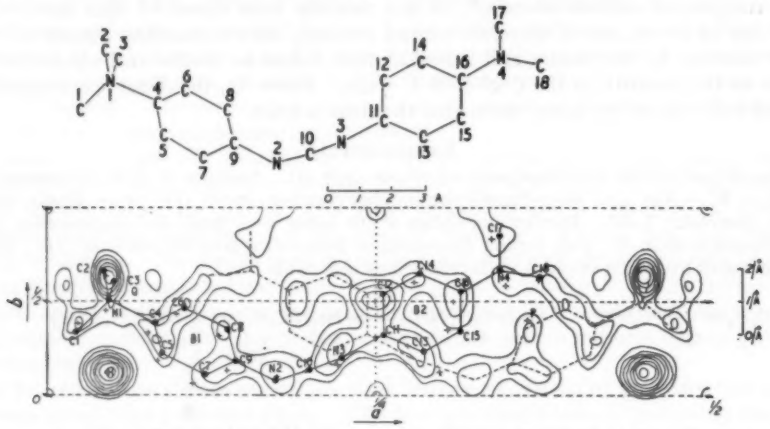
XUM

Attempts to find the structure of bis-*p*-dimethylaminophenylcarbodi-imide were unsuccessful and a heavy atom was introduced into this molecule in an attempt to simplify the analysis.

Multiple-film Weissenberg photographs of the *hk*0 and *h*0*l* reflexions from the monomethiodide (V) crystals were taken with Cu-$K_\alpha$ radiation. The intensities were estimated visually by means of a calibration strip. The systematic absences (0*kl*) with *l* odd and (*h*0*l*) with *h* odd give the possible space-groups $Pca2_1$ or *Pcam*. If *Pcam* were correct the molecules would lie on special positions, and, since the monomethiodide cannot possess a centre of symmetry or a twofold axis, the only possibility is that it has a mirror plane. The unit-cell dimensions suggest that this is unlikely. The space-group was confirmed to be No. 29 $Pca2_1$ ($C^5_{2v}$) by plots of the intensity distribution of the (*h*0*l*) and (*hk*0) projections.[9] (*hk*0) was found to have a centric and (*h*0*l*) a non-centric distribution. The calculated linear absorption coefficient is 145 cm.$^{-1}$. Since the maximum path length of the *X*-rays through the plate-like crystal in the two projections was $1{\cdot}75 \times 10^{-3}$ cm., absorption errors did not exceed 20% of the observed intensities and were ignored.

The intensities were put on an approximately absolute scale by means of a Wilson plot [10] which gave a value of $B = 3{\cdot}8$ Å. This value of the temperature factor was retained throughout the analysis.

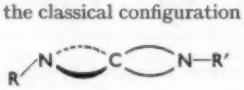
*Electron density* $\rho(xy0)$ *contours at arbitrary intervals. Zero contour is at* 3·5 *e per* Å$^2$. *The contours for the iodine atom are at ten times the interval of those of the other atoms.*



*The* X-*Ray Analysis.*—Initial values of the parameters of the iodine atom ($x/a = 0{\cdot}047$ $y/b = 0{\cdot}119$, $z/c = 0{\cdot}250$) were found from the Patterson functions P($XY0$) and P($X0Z$). Structure factors were then calculated for the iodine atom alone and were found to give a preliminary *R* value of 0·25 and 0·26 for (*hk*0) and (*h*0*l*) respectively. *R*, the so-called " agreement index," is the residual

$$\sum \big|\, |F_o| - |F_c| \,\big| / \sum |F_o|$$

The signs given by the iodine atom were then used to calculate a Fourier synthesis for the centrosymmetric (*hk*0) projection, all but one of the 75 observed planes being included. As a model with a linear central C–N=C=N–C chain could not be fitted to this Fourier map, atomic positions based on a molecule with the classical configuration



were used to calculate another set of structure factors. The residual immediately fell to 0·19. The Figure shows the second Fourier map which is based on all 75 structure factors. The positions of the atoms assumed at this stage are shown by crosses.

[9] Howells, Phillips, and Rogers, *Acta Cryst.*, 1950, **3**, 210.
[10] Wilson, *Nature*, 1942, **150**, 152.

All the signs of the structure factors were now known and Fourier difference maps were used for further refinement. The first of these indicated that a methyl group assumed to be at *P* was in the wrong position and should be moved to *Q* (*C*3), thus transferring the quarternary nitrogen atom to the other end of the molecule, closer to the iodide ion. After a few more cycles it became evident that four reflexions (800; 10,00; 12,00; and 510) were affected by extinction. These four reflexions have similar values of sin θ (about 0·17) and there are no

TABLE 1. *Final* x *and* y *parameters.*

| | *x*/*a* | *y*/*b* | | *x*/*a* | *y*/*b* | | *x*/*a* | *y*/*b* | | *x*/*a* | *y*/*b* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | 0·0465 | 0·116 | C6 | 0·106 | 0·462 | C12 | 0·256 | 0·539 | C18 | 0·374 | 0·630 |
| C1 | 0·024 | 0·326 | C7 | 0·121 | 0·103 | C13 | 0·285 | 0·233 | N1 | 0·048 | 0·500 |
| C2 | 0·044 | 0·660 | C8 | 0·137 | 0·354 | C14 | 0·283 | 0·650 | N2 | 0·174 | 0·072 |
| C3 | 0·052 | 0·600 | C9 | 0·144 | 0·187 | C15 | 0·314 | 0·340 | N3 | 0·224 | 0·200 |
| C4 | 0·083 | 0·387 | C10 | 0·200 | 0·132 | C16 | 0·314 | 0·553 | N4 | 0·343 | 0·667 |
| C5 | 0·088 | 0·233 | C11 | 0·256 | 0·329 | C17 | 0·343 | 0·852 | | | |

TABLE 2. *Observed and calculated structure factors.* (*Figures are absolute values.*)

| *h* | *k* | $F_o$ | $F_c$ | *h* | *k* | $F_o$ | $F_c$ | *h* | *k* | $F_o$ | $F_c$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 0 | — | 76·0 + * | 0 | 1 | 27·6 | 29·2 + | 0 | 2 | 37·6 | 48·0 − |
| 4 | 0 | 36·4 | 51·2 + | 1 | 1 | 97·6 | 110·8 + | 1 | 2 | 88·8 | 94·4 + |
| 6 | 0 | 28·0 | 33·6 − | 2 | 1 | 82·0 | 86·5 + | 2 | 2 | 0·0 | 38·8 + |
| † 8 | 0 | (104·0 | 144·0) − | 3 | 1 | 68·8 | 64·0 + | 3 | 2 | 112·0 | 107·2 + |
| † 10 | 0 | (172·9 | 220·4) − | 4 | 1 | 27·2 | 26·0 + | 5 | 2 | 139·6 | 143·2 + |
| † 12 | 0 | (150·4 | 183·2) − | † 5 | 1 | (115·6 | 140·0) + | 7 | 2 | 144·8 | 146·4 + |
| 14 | 0 | 102·4 | 106·4 − | 6 | 1 | 36·8 | 24·4 + | 9 | 2 | 76·4 | 68·0 + |
| 18 | 0 | 75·6 | 72·4 + | 7 | 1 | 55·2 | 65·6 + | 13 | 2 | 109·2 | 113·2 − |
| 20 | 0 | 111·6 | 117·6 + | 8 | 1 | 89·2 | 86·0 − | 14 | 2 | 48·0 | 52·8 − |
| 22 | 0 | 126·0 | 130·0 + | 9 | 1 | 38·4 | 28·0 + | 15 | 2 | 133·6 | 125·2 − |
| 24 | 0 | 87·2 | 90·4 + | 10 | 1 | 90·0 | 84·8 − | 16 | 2 | 51·2 | 37·6 + |
| 28 | 0 | 37·6 | 33·7 − | 11 | 1 | 26·4 | 26·4 + | 17 | 2 | 120·8 | 131·2 + |
| 30 | 0 | 92·4 | 95·2 − | 12 | 1 | 86·4 | 90·8 − | 19 | 2 | 55·6 | 52·4 − |
| 32 | 0 | 64·8 | 59·6 − | 13 | 1 | 36·8 | 41·6 − | 20 | 2 | 29·6 | 21·6 + |
| 34 | 0 | 60·0 | 59·2 − | 14 | 1 | 35·6 | 34·4 − | 23 | 2 | 43·2 | 35·6 + |
| | | | | 15 | 1 | 49·6 | 62·8 − | 25 | 2 | 86·0 | 81·6 + |
| 0 | 3 | 78·0 | 62·0 − | 17 | 1 | 46·0 | 46·4 − | 27 | 2 | 79·6 | 83·2 + |
| 2 | 3 | 56·0 | 47·2 − | 18 | 1 | 66·0 | 59·2 + | 29 | 2 | 62·0 | 56·8 + |
| 3 | 3 | 87·2 | 84·4 + | 19 | 1 | 58·0 | 57·2 − | | | | |
| 5 | 3 | 67·6 | 66·8 + | 20 | 1 | 46·0 | 52·0 + | 0 | 4 | 108·8 | 102·4 − |
| 7 | 3 | 85·6 | 79·2 + | 21 | 1 | 35·6 | 36·8 − | 2 | 4 | 68·4 | 60·8 + |
| 8 | 3 | 53·6 | 46·0 + | 22 | 1 | 63·6 | 62·8 + | 8 | 4 | 58·8 | 50·4 + |
| 9 | 3 | 26·0 | 32·0 + | 23 | 1 | 39·2 | 41·6 + | 10 | 4 | 68·8 | 74·8 + |
| 10 | 3 | 55·2 | 49·2 + | 24 | 1 | 57·6 | 54·4 + | 12 | 4 | 66·8 | 70·8 + |
| 12 | 3 | 56·0 | 58·0 + | 25 | 1 | 53·2 | 50·8 + | | | | |
| 13 | 3 | 38·4 | 34·8 − | | | | | | | | |
| 14 | 3 | 30·4 | 28·0 + | | | | | | | | |
| 15 | 3 | 77·6 | 79·2 − | | | | | | | | |
| 17 | 3 | 61·6 | 61·1 − | | | | | | | | |
| 18 | 3 | 26·8 | 36·0 − | | | | | | | | |
| 19 | 3 | 33·2 | 39·2 − | | | | | | | | |
| 20 | 3 | 47·2 | 55·2 − | | | | | | | | |

* sin θ too low for observation. † Extinguished planes.

planes of lower sin θ with such large intensities. These planes were omitted from subsequent refinement cycles, during which the *R* factor fell to 0·09. The final atomic positions are shown by circles in the Figure. The symmetry-related molecule is shown by broken lines. Table 1 gives the final atomic parameters and Table 2 the observed and calculated structure factors. Since the projection shows that the molecule is bent it was decided not to proceed further with the analysis.

## DISCUSSION

The following conclusions about the geometry of the molecule can be drawn from the Figure:

(i) The two bonds to N2 are not collinear.

(ii) Those to N3 are approximately collinear in projection, but the shortness of the projected length of N2=C10=N3 (approximately 2·1 Å) shows that these two bonds are

considerably inclined to the plane of projection. On the other hand, the approximate regularity of the benzene ring B2 and the normal lengths of the N3–C11 and N4–C16 bonds (1·4 Å) show that these are all approximately parallel to the plane of projection. Thus the C10–N3–C11 system cannot be linear and moreover it does not lie in the plane of the C9–N2–C10 system.

(iii) The plane of the benzene ring B2 is nearly perpendicular to the plane of C10–N3–C11. The angle between B1 and C9–N2–C10 cannot be estimated very accurately but it is easy to see that it is large.

These results show that the molecule has the asymmetric form predicted by classical stereochemistry. Equal numbers of right- and left-handed forms of the molecule occur in the crystal.

The non-coplanarity of the $-C_6H_4-N=C=$ systems resembles that which occurs in *cis*-azobenzene [11] and suggests that there is no conjugation between the central double-bond system and the benzene rings. A carbodi-imide therefore cannot help to discriminate between the two possible effects (electronegativity and hyperconjugation) which, according to Bullough and Wheatley,[5] might account for the linearity of vinylideneamines.

We thank Professor E. G. Cox, who suggested this investigation, for many helpful discussions, and for putting at our disposal research facilities provided by the Royal Society and Imperial Chemical Industries Limited. We are indebted to Sir Alexander Todd for some of the material used in the investigation.

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[*Received, December 9th*, 1957.]

[11] Hampson and Robertson, *J.*, 1941, 409.

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## 394. *The Structure of* Brachychiton diversifolium *Gum* (Sterculia caudata).

By E. L. HIRST, ELIZABETH PERCIVAL, and R. S. WILLIAMS.

The gum exudate from *Brachychiton diversifolium* is an acetylated acidic polysaccharide which contains rhamnose (1 part), galactose (1 part), and glucuronic acid (2 parts). Graded hydrolysis of the gum gives D-glucurone, an aldobiuronic acid, identified as 2-*O*-α-D-glucuronosyl-L-rhamnose, and unidentified oligosaccharides of high uronic acid content.

The methylated gum gives on hydrolysis 2 : 3 : 4 : 6-tetra-*O*-methyl- and 2 : 3 : 6-tri-*O*-methyl-D-galactose, 3 : 4-di-*O*-methyl- and 3-*O*-methyl-L-rhamnose, 2 : 3 : 4-tri-*O*-methyl-D-glucuronic acid, and a mixture of methylated uronic acids.

THROUGH the kindness of Mr. V. Grenning, Director of Forests in Queensland, Australia, a sample of gum from *Brachychiton diversifolium* collected in the Atherton district of Northern Queensland was made available for study. This tree was formerly known as *Sterculia caudata*. Gum exudates of the *Sterculia* trees previously examined [1] have been found to be polymers of rhamnose, galactose, and galacturonic acid residues, partly acetylated in two instances at least. The gum from *Sterculia setigera* also contains residues of tagatose. The three species so far investigated, *S. urens*, *S. tormentosa*, and *S. setigera*, are, however, all characterised by a high uronic acid content and are consequently very resistant to hydrolysis.

Investigation of three separate nodules of *Brachychiton* exudate indicated that the sample was essentially homogeneous, and contained residues of galactose, rhamnose, and glucuronic acid. Traces of xylose and arabinose were also present in the crude gum, and

[1] Beauquesne, *Compt. rend.*, 1946, **222**, 1056; Hirst, Hough, and Jones, *J.*, 1949, 3145; Hough and Jones, *J.*, 1950, 1199; Rao and Sharma, *Proc. Indian Acad. Sci.*, 1957, **45**, *A*, 24.

were detected in large-scale work on the pure polysaccharide. The proportions present, however, are so low they can have very little structural significance. It was noticeable that gum contaminated with bark had more pentoses than did the purer sample. The presence of ash (4·1%) was due at least in part to metal salts of the uronic acid; the aqueous mucilage was neutral to litmus and non-reducing to Fehling's solution. The small amount of methoxyl (1·4%) was present as methyl ester since the purified polysaccharide, isolated after alkaline treatment of the gum, was free from methoxyl groups. The acetyl content (19·3%) resembled that of *Sterculia setigera* [1] and *Cochlospermum gossypium*.[2]

The gum was slightly soluble in water from which it was best precipitated with acetone. Three extracts were obtained of identical composition. Further attempts at fractionation by dissolution of the gum in alkali and precipitation of the " free-acid " form by addition of ethanol were unsuccessful. These results are in harmony with the electrophoretic behaviour of the pure polysaccharide in a borate buffer at pH 10, where a single peak was obtained.

The purified gum, $[\alpha]_D$ +69°, had an equivalent weight of 342 and a uronic anhydride content of 50·1% (calculated for a substance of equivalent weight of 342, 51·5%). The proportion of uronic anhydride is unusually high for a plant gum, but finds parallels in *Sterculia setigera* [1] gum and *Khaya grandfolia* [3] gum. In keeping with this high uronic acid content, and the extreme stability of the glycosiduronic acid linkage, the material was very resistant to hydrolysis. Complete hydrolysis was accompanied by degradation: the solutions invariably darkened during hydrolysis and the yield of hydrolysate was never higher than 80%.

Although a complete quantitative hydrolysis was impossible, estimation [4,5] of the neutral sugars indicated the presence of approximately equal amounts of galactose and rhamnose. The quantity of rhamnose was substantiated by determination [6] of the proportion (24%) of this sugar in the unhydrolysed polysaccharide. A partial hydrolysate (N-sulphuric acid at 100° for 7 hr.), after neutralisation with barium hydroxide, was concentrated to an amorphous solid (A) consisting of neutral sugars and barium uronates (B). The neutral sugars were extracted with methanol and partitioned on a cellulose column. Crystalline L-rhamnose (3·2% of the original weight of gum) and D-galactose (10%) were separated, and further characterised as crystalline derivatives. On further hydrolysis, the acidic fraction (B) (72% of the original weight of gum) liberated more galactose and rhamnose.

Conversion of the hydrolysate (A), after de-ionisation, into the methyl ester methyl glycoside, reduction with potassium borohydride, and hydrolysis gave a syrup (C) containing galactose, rhamnose, and glucose (paper chromatography), the last being eliminated by treatment of the hydrolysate with D-glucose oxidase. Partition of syrup (C) on a paper column led to the isolation and characterisation of the following sugars in the approximate proportions given: rhamnose (27·5%), galactose (54%), and glucose (18·5%). An alternative method of estimation [4,7] of the proportions of the sugars present in syrup (C) gave rhamnose (24%), galactose (58%), and glucose (17·7%); these figures are in reasonable agreement with the amount of the sugars separated from this syrup. As glucose was not found in any of the gum hydrolysates, it was not present in the original gum, and the glucose isolated from syrup (C) was clearly produced by reduction of glucuronic acid residues by potassium borohydride. Support for this deduction was obtained by the separation and characterisation (as the crystalline *p*-nitroaniline derivative) of glucurone from the acid fraction of the gum hydrolysate.

[1] Hirst and Dunstan, *J.*, 1953, 2332.
[2] Aspinall, Hirst, and Matheson, *J.*, 1956, 989.
[3] Hirst and Jones, *J.*, 1949, 1659.
[4] Pridham, *Analyt. Chem.*, 1956, **28**, 1967.
[5] Dische and Shettles, *J. Biol. Chem.*, 1948, **175**, 595.
[6] Manners, unpublished work.

The presence of D-glucuronic acid in *Brachychiton diversifolium* exudate is in contrast to the positions with the other species of *Sterculia* gums examined, with *Cochlospermum gossypium*, and with *Khaya grandifolia*, all of which contain D-galacturonic acid, although the last of these contains in addition 4-*O*-methyl-D-glucuronic acid. The possible presence of galacturonic acid was considered and the question was raised whether the higher proportion of galactose found in the reduced syrup (C) compared with the amount estimated in the gum hydrolysate might have been produced by reduction of galacturonic acid residues. However, no evidence could be obtained for the presence of this acid in any of the gum hydrolysates by chromatography, by standard colour tests, or by the isolation of mucic acid from the oxidised acid hydrolysate. It might be argued that the inability to isolate free galacturonic acid was due to its degradation under the hydrolytic conditions used since Fischer and Dorfel [8] record 77% and 97% destruction of galacturonic acid by N-hydrochloric acid at 100° in 20 and 40 hours respectively. Against this argument, however, is the fact that the present authors failed to isolate any oligosaccharides or methylated oligosaccharides containing galacturonic acid residues from partial acid hydrolysates of the gum or methylated gum respectively. The present indications are that galacturonic acid residues, if present in the gum, are only there in very small proportion and have escaped detection.

The gum was converted into its fully methylated derivative (OMe, 42·3%) which, like the parent material, was extremely resistant to hydrolysis. Methanolysis with 8% methanolic hydrogen chloride and then with aqueous hydrochloric acid yielded 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (12 parts), 3 : 4-di-*O*-methyl-L-rhamnose (1 part), 2 : 3 : 6-tri-*O*-methyl-D-galactose (10 parts), 3-*O*-methyl-L-rhamnose (4 parts) (characterised as crystalline derivatives), and a mixture of methylated barium uronates (69% of the hydrolysate). The barium uronates were hydrolysed further with 2N-sulphuric acid, and the product was separated into three fractions. Each fraction was converted into the methyl ester methyl glycoside, reduced with lithium aluminium hydride, and hydrolysed. From fraction U1 2 : 3 : 4-tri-*O*-methyl-D-glucose and 3 : 4-di-*O*-methyl-L-rhamnose were separated. The former was characterised by its analytical constants and as the *N*-phenyl-D-glucosylamine, and the latter by its analytical constants, demethylation, electrophoretic mobility, and oxidation with potassium periodate.[9] As tri-*O*-methylglucose was not present among the neutral sugars isolated on direct hydrolysis of the methylated gum, it must have arisen by reduction of 2 : 3 : 4-tri-*O*-methyl-D-glucuronic acid. The hydrolysates from the second and third fractions both contained 2 : 3 : 4-tri-*O*-methyl-D-glucose, 3-*O*-methyl-L-rhamnose, rhamnose, and a mono-*O*-methylhexose. In addition, the third fraction contained 2 : 3 : 6-tri-*O*-methylgalactose and a di-*O*-methylhexose (paper chromatography).

The hydrolysate of the methylated, reduced, remethylated polysaccharide was found to contain 2 : 3 : 4 : 6-tetra-*O*-methylglucose in addition to all the methylated derivatives found above (paper chromatography).

Attempted fractionation of the partly hydrolysed acidic material (B) on an ion-exchange resin column gave pure fractions corresponding to glucurone and an aldobiuronic acid. The aldobiuronic acid, $[\alpha]_D$ +63°, gave rhamnose and glucuronic acid (paper chromatography) on hydrolysis and had the correct equivalent weight (332) for an aldobiuronic acid containing these two sugar residues. Reduction with potassium borohydride eliminated rhamnose, indicating that the free reducing group was carried by this sugar. Conversion of the aldobiuronic acid into the methyl ester methyl glycoside, reduction, and remethylation gave a methylated disaccharide which on hydrolysis and separation of the hydrolysate on thick paper gave 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose and 3 : 4-di-*O*-methyl-L-rhamnose, both sugars being identified by chromatography, ionophoresis, and demethylation. A trace of a third component corresponding chromatographically

[8] Fischer and Dorfel, *Z. physiol. Chem.*, 1955, **301**, 224; **302**, 186.
[9] Butler, Lloyd, and Stacey, *J.*, 1955, 1531.

to a tri-*O*-methylhexose was considered to have arisen through under-methylation. These results indicate that the aldobiuronic acid is 2-*O*-α-D-glucuronosyl-L-rhamnose. This is supported by the isolation of 3 : 4-di-*O*-methyl-L-rhamnose from the hydrolysate of the methylated polysaccharide, and of 2 : 3 : 4-tri-*O*-methyl-D-glucose from the reduced methylated uronic acids, and the chromatographic detection of 2 : 3 : 4 : 6-tetra-*O*-methylglucose in the hydrolysate of the methylated, reduced, and remethylated polysaccharide. Although 2-*O*-galacturonosyl-L-rhamnose has been isolated from other plant gums,[2,3,10] and from okra mucilage,[11] this is the first reported isolation of glucuronic acid glycosidically linked to $C_{(2)}$ of L-rhamnose.

It is not possible to formulate a unique molecular structure for the gum. The monomethylrhamnose isolated from the hydrolysate of the methylated polysaccharide and the free rhamnose, and di- and mono-*O*-methylhexoses in the methylated acidic hydrolysate, must have arisen from residues which were triply linked in the gum. It is clear, therefore, that the gum possesses a highly branched structure with galactose and glucuronic acid residues at the ends of the branches. Sugar residues, the presence of which has been definitely established, are:

$$\cdots \text{Ga 1}-\cdots \quad \cdots -4\ \text{Ga 1}-\cdots \quad \cdots -2\ \text{Rh 1}-\cdots \quad \cdots -4\ \underset{\displaystyle 2}{\text{Rh 1}}-\cdots \quad \cdots \text{GA 1}-\cdots$$

(Ga = D-galactopyranose, Rh = L-rhamnopyranose, GA = D-glucopyruronic acid).

The isolation and characterisation of an aldobiuronic acid indicate that the residue GA 1–2 Rh is also a structural feature of the gum.

## Experimental

*Analytical Methods.*—All solutions were evaporated under reduced pressure below 60°. Unless otherwise stated, hydrolyses were done with 2N-sulphuric acid for 24 hr. at 100°. The cooled hydrolysates were neutralised with barium carbonate, and the filtrates concentrated to syrups. Paper-partition chromatography was carried out on Whatman No. 1 paper at a constant temperature of 20° with the upper layers of the following solvent systems (v/v): (1) butan-1-ol–benzene–pyridine–water (5 : 1 : 3 : 3); (2) ethyl acetate–pyridine–water (10 : 4 : 3); (3) butan-1-ol–ethanol–water (4 : 1 : 5); (4) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4); (5) butan-1-ol–acetic acid–water (4 : 1 : 5); (6) benzene–ethanol–water (169 : 47 : 15); (7) ethyl methyl ketone half saturated with water plus ammonia (99 : 1). Papers were sprayed with saturated aqueous solution of aniline oxalate, and 3% *p*-anisidine hydrochloride in butan-1-ol containing a little stannous chloride. $R_G$, $R_{Gal.}$, and $R_F$ are the rates of travel relative to tetramethylglucose, galacturonic acid, and the solvent front respectively. Electroionophoresis [12] was carried out in borate buffer of pH 10. Whatman 3MM sheets after preliminary extraction with hot benzene–ethanol (1 : 1) were used for the chromatographic separation of small amounts of material. Specific rotations were measured in water at 18°.

*Preliminary Examination of the Gum.*—The gum, obtained as light-brown translucent nodules, was contaminated with bark and had a resinous odour. Three separate nodules were powdered, dried to constant weight over phosphoric oxide at 60° (loss 17%), and analysed. They were not significantly different in composition and had ash 4·1; N, 0; OMe, 1·4; AcO, 19·3%. Chromatography of acid hydrolysates (solvent 1) revealed spots corresponding in position and colour with glucurone, rhamnose, galactose, and barium uronates, the last remaining at the starting line.

*Purification and Attempted Fractionation of the Material.*—(1) Repeated extraction of the crude gum with water and precipitation of the polysaccharide from each extract by the addition of acetone gave identical fractions (paper chromatography of the hydrolysates).

(2) The crude material (4 g.) was dissolved in chilled N-sodium hydroxide (200 c.c.) in an atmosphere of nitrogen. After acidification (pH 2) of the solution with 50% hydrochloric

[10] Hirst, Hough, and Jones, *J.*, 1949, 3145.
[11] Whistler and Conrad, *J. Amer. Chem. Soc.*, 1954, **76**, 3544.
[12] Foster, *Chem. and Ind.*, 1952, 1050.

acid, and removal of fragments of bark at the centrifuge, the polysaccharide was precipitated in four fractions by the gradual addition of ethanol (1·3 vols. gave 1·81 g.; 2 vols., 0·30 g.; 5 vols., 0·06 g.; 7 vols., 0·03 g.). Each fraction, freed from chloride ion by trituration with ethanol, was washed with ether and dried over phosphoric oxide (60°/12 mm.) to constant weight. Chromatography of the hydrolysate of each fraction (solvent 1) showed spots identical with those given by the crude gum. Very faint spots corresponding to xylose and arabinose were also detected from the last two fractions.

The recombined fractions were dissolved in water, and the polysaccharide, precipitated with ethanol (3 volumes), was washed and dried as before. It was a white fibrous material (2·2 g.) which had $[\alpha]_D$ +69° (*c* 0·4 in N-NaOH) [Found: equiv., 342 (by titration): uronic anhydride, 50·1 (by decarboxylation); ash, 0·83%; AcO, 0; OMe, 0). A portion (0·05 g.) in borate buffer of pH 10 (10 c.c.) gave a symmetrical peak when examined in the Antweiler micro-electrophoresis apparatus (1·5 mA, 35 V, 10 min.). Autohydrolysis of the polysaccharide for 24 hr. at 100° showed traces of galactose and rhamnose in the concentrated hydrolysate. After hydrolysis with N-sulphuric acid at 100° for 13 hr. ($[\alpha]_D$ +104°, 2 hr. ⟶ +77°, 13 hr.) the solution still contained unhydrolysed polysaccharide. Heating with 2N-sulphuric acid at 100° for 24 hr. was necessary to hydrolyse the polysaccharide completely. The solution then became dark brown and it was necessary to decolorise the neutralised filtrate with charcoal. Quantitative estimation, by the method of Hirst and Jones,[4] of the sugars produced on complete acid hydrolysis of the gum gave, after allowance for a uronic anhydride content of 50%, a 60% recovery of neutral sugars (calc. as percentage of anhydro-sugars in the original gum) comprising 23·5% of rhamnose and 26·5% of galactose. Pridham's colorimetric method [5] gave the proportion of galactose : rhamnose = 1 : 1·09. After allowance for the uronic acid present, this corresponds to 23·8% of anhydrogalactose and 26·0% of anhydrorhamnose in the gum. Colorimetric estimation of rhamnose by the method of Dische and Shettles [6] gave 23·9% of anhydrorhamnose in the purified gum.

*Partial Hydrolysis of the Gum and Characterisation of the Neutral Sugars.*—The purified gum (9·45 g.) was heated at 100° with N-sulphuric acid (500 c.c.) for 7 hr. The cooled solution was made slightly alkaline with barium hydroxide solution, the excess of alkali being removed immediately with carbon dioxide and the filtrate concentrated to a solid (A) consisting of neutral sugars and barium uronates. The cold aqueous extracts of this material were poured into well-stirred methanol (10 volumes). The precipitated barium salts were exhaustively extracted with hot methanol, and the total methanolic liquors evaporated to a syrup (3·11 g.). The barium uronates (B) (5·38 g.) were left as an amorphous solid. The syrup was fractionated on a cellulose column [13] (85 × 2·7 cm.) with butan-1-ol two-thirds saturated with water as the eluant:

Fraction 1 (1·125—2·175 l.) (0·021 g.), $R_F$ 0·78 (solvent 1), gave a positive Selivanoff reaction.

Fraction 2 (2·325—2·925 l.): L-rhamnose (0·26 g.), $R_F$ variable but identical with that of authentic rhamnose, $[\alpha]_D^{20}$ +8·4° (*c* 1·0). Recrystallisation from butan-1-ol gave L-rhamnose hydrate, m. p. and mixed m. p. 88—89°. The benzoylhydrazone [10] had m. p. and mixed m. p. 186—189°.

Fraction 3 (2·930—6·225 l.) (0·046 g.), $R_F$ 0·34—0·39. Three components were observed in this fraction (paper chromatography) corresponding to rhamnose, xylose, and arabinose. Visual inspection suggested that rhamnose comprised the bulk of the fraction.

Fraction 4 (8·250—12·027 l.): D-galactose (0·951 g.), m. p. and mixed m. p. 163—165°, $[\alpha]_D^{20}$ +83° (*c* 3·5). The diethyl mercaptal [14] had m. p. and mixed m. p. 140—141°.

Fraction 5 (1·43 g.), eluted partly with butan-1-ol–acetic acid–water (4 : 1 : 5) and finally with water, was added to the amorphous barium uronates (B) (total yield 6·81 g.).

*Isolation and Characterisation of Glucose after Reduction of the Polysaccharide Hydrolysate.*—The mixture of neutral sugars and barium uronates (A) (8·2 g.), after de-ionisation with ion-exchange resin (Amberlite IR-120, $H^+$ form), was refluxed with 4% methanolic hydrogen chloride for 6 hr. The neutralised filtrate gave on evaporation a solid which was dissolved in water (50 c.c.) and added slowly with stirring to a solution of potassium borohydride (4 g.) in water (60 c.c.). After 2 hr. excess of acetic acid was added and ions were removed on a mixed-bed resin column (Amberlite IR-120 $H^+$ and IR-4B, $OH^-$). The eluant was evaporated to

[13] Hough, Jones, and Wadman, *J.*, 1949, 2511.
[14] Wolfrom, *J. Amer. Chem. Soc.*, 1930, **52**, 2466.

dryness, traces of borate being removed by repeated evaporation with methanol. The derived syrup (5·1 g.) was heated at 100° with N-sulphuric acid for 7 hr. Neutralisation of the cooled solution, with barium carbonate, filtration, and evaporation gave a syrup (C) (4·4 g.) containing glucose, galactose, and rhamnose (paper chromatography). Glucose was eliminated on treatment of the syrup (C) (10 mg.) with the specific enzyme D-glucose oxidase. Partition of the syrup (C) (2·19 g.) on a Grycksbo filter paper column (LKB 3391) eluted with butan-1-ol undersaturated with water (prepared by saturating butan-1-ol with water at 0° and allowing the separated organic phase to warm to room temperature) gave:

Fraction (*a*): L-Rhamnose (0·508 g.), characterised as the 2 : 5-dichlorophenylhydrazone, m. p. and mixed m. p. 171°.

Fraction (*b*): D-Glucose (0·150 g.), m. p. and mixed m. p. [after recrystallisation of the isolated material and of authentic D-glucose from ethanol and light petroleum (b. p. 100—120°)] 148—149°, $[\alpha]_D$ +53° (*c* 0·70).

Fraction (*c*): D-Galactose (0·631 g.), characterised as the 2 : 5-dichlorophenylhydrazone, m. p. and mixed m. p. 196—197°. An overlap fraction (0·563 g.) containing galactose and glucose (2 : 1) (paper chromatography, visual estimation) was also separated.

The quantity of glucose in syrup (C) was estimated by determination of the reducing power [15] before and after treatment with D-glucose oxidase [7] (commercial " Dee-O " manufactured by the Takamine Corporation), an enzyme which catalyses the oxidation of glucose to the non-reducing gluconic acid.[16] Synthetic mixtures containing glucose (*a*) 0·25 mg., (*b*) 0·41 mg., galactose (*a*) 1·49 mg., (*b*) 1·30 mg., and rhamnose (*a*) 0·60 mg., (*b*) 0·55 mg. per 5·0 c.c. portion, and the syrup C (2·26 mg. in 5·0 c.c. of water) were each treated with D-glucose oxidase (7·5 mg. in water 1 c.c.) for 3 hr. at 36°. As it was necessary to deproteinise the mixture before measuring the reducing power the mixture was then treated with water (0·40 c.c.), zinc sulphate solution (0·30 c.c.), and barium hydroxide solution (0·30 c.c.) which had been prepared according to Nelson's directions.[17] The precipitate was removed on the centrifuge, a portion of the supernatant solution (5·00 c.c.) withdrawn, and its reducing power estimated. A " blank " determination was carried out simultaneously in the same manner, except that the enzyme was inactivated by heating it at 100° for 10 min. before use. Reducing powers are expressed as c.c. of 0·01N-sodium thiosulphate and in each instance have been calculated so as to refer to a 5 c.c. aliquot part of the original solution:

| | (*a*) | (*b*) | C |
|---|---|---|---|
| Reducing power of " blank " (c.c.) | 6·55 | 6·41 | 5·29 |
| Reducing power of incubated solution (c.c.) | 5·65 | 4·90 | 3·98 |
| Decrease in reducing power after incubation (c.c.) | 0·90 | 1·51 | 1·31 |
| Glucose (mg.) per 5·0 c.c. | 0·26 | 0·44 | 0·39 |

Hence the syrup (C) contained 17·7% (average of two determinations) of glucose.

Quantitative estimation [4] of the rhamnose and total hexose in syrup (C) gave 24·2 and 75·8% respectively.

Syrup (C), therefore, comprises D-glucose 17·7, L-rhamnose 24·2, and D-galactose 58·1%. The syrup had $[\alpha]_D$ +55° (*c* 1·1). The above composition requires $[\alpha]_D$ +58°.

*Examination and Fractionation of the Uronic Acids on Ion-exchange Resin.*—The free uronic acids (D) (4·66 g.) obtained by treatment of the barium salts (B) (6·81 g.) with ion-exchange resin (Amberlite IR-120 $H^+$) had equivalent weight 338. Complete hydrolysis of the acids (D) (20 mg.) liberated more rhamnose and galactose (paper chromatography).

A column of anion-exchange resin (Amberlite IRA-400, acetate form) was prepared,[18] and the uronic acids (D) (3·39 g.) were absorbed on it. After removal of neutral sugars (0·074 g.) by elution with water, the acids were removed with increasing concentrations of aqueous acetic acid. Only two pure fractions were obtained; four other fractions were isolated but paper chromatography showed them to be mixtures of oligosaccharides which on hydrolysis gave galactose, rhamnose, and glucuronic acid:

Fraction E (0·008 g.), eluted with 2—3% acetic acid, was chromatographically identical with glucurone.

[15] Shaffer and Sömogyi, *J. Biol. Chem.*, 1933, **100**, 695; Hanes and Cattle, *Proc. Roy. Soc.*, 1938, *B*, **125**, 387.
[16] Keilin and Hartree, *Biochem. J.*, 1948, **42**, 230.
[17] Nelson, *J. Biol. Chem.*, 1944, **153**, 375.
[18] Matheson, Ph.D. Thesis, Edinburgh, 1955.

Fraction F (0·355 g.), eluted with 3·5—5% acetic acid, had $[\alpha]_D$ +63° (*c* 1·5), $R_{Gal.}$ 0·24, $M_G$ 0·72 [Found: equiv., 332 (by titration)]. Complete acid-hydrolysis gave rhamnose and glucuronic acid (paper chromatography). Partial hydrolysis, by N-sulphuric acid at 100° for 4 hr., gave rhamnose, glucuronic acid, and unhydrolysed material. Reduction by aqueous sodium borohydride followed by hydrolysis, neutralisation, and de-ionisation gave a product containing only glucuronic acid (paper chromatography). Methylation of Fraction E (0·320 g.) three times with 40% aqueous sodium hydroxide (7·5 c.c.) and dimethyl sulphate (3·0 c.c.) in an atmosphere of nitrogen at room temperature was follwed by two further methylations, one at 50° and another at 70°. After acidification, the solution was extracted with cold chloroform. Removal of the chloroform gave a syrup (0·148 g.) which was methylated with methyl iodide (2·3 c.c.) and silver oxide (1·2 g.) under reflux. The product (0·140 g.), dissolved in dry methylal (2·0 c.c.), was reduced with lithium aluminium hydride (0·1 g. in 1 c.c. of methylal). Excess of reagent was destroyed by cautious addition of water and the product (0·098 g.) isolated by methylal-extraction. Two further methylations with Purdie's reagents gave a syrup (0·088 g.) which was hydrolysed by N-sulphuric acid at 100° for 6 hr., and the product (0·060 g.) was separated on thick paper with solvent (3). The first component was identical with 2 : 3 : 4 : 6-tetra-*O*-methylglucose chromatographically and ionophoretically. Demethylation gave glucose. The second component was identical with 3 : 4-di-*O*-methylrhamnose chromatographically and ionophoretically ($M_G$ 0·36). Demethylation gave rhamnose. A very small quantity of a third component ($R_G$ 0·76) gave glucose on demethylation.

*Isolation of Glucurone after Complete Hydrolysis of the Polysaccharide.*—Free uronic acids (0·20 g.) isolated as before from a completely hydrolysed sample of the gum were separated on sheets of thick paper (solvent 4) into two fractions:

Fraction 1 (0·039 g.) was chromatographically identical with glucurone. The derived yellow crystalline *p*-nitroaniline derivative [19] (0·020 g.) had m. p. and mixed m. p. 128—130° (after recrystallisation from methanol).

Fraction 2 (0·116 g.) had $[\alpha]_D$ +33·6° (*c* 1·16) and gave a single spot on chromatography identical with glucuronic and/or galacturonic acid. Treatment with basic lead acetate [20] gave a yellow-brown precipitate similar to that given by authentic glucuronic acid and distinct from the brick-red precipitate given by a control sample of galacturonic acid. A portion (0·10 g.) in water was oxidised with bromine (1 c.c.) for 4 days at 30—35° (nitric acid oxidation was avoided because it would convert any trace of galactose, which might have persisted in this fraction, into mucic acid). The residue obtained after removal of bromine by aeration and evaporation of the solution to dryness was dissolved in N-sodium hydroxide. Filtration followed by acidification of the filtrate by dropwise addition of hydrochloric acid failed to yield mucic acid even on prolonged storage.

*Methylation of the Polysaccharide.*—The pure polysaccharide (22 g.) was dissolved in 30% sodium hydroxide solution (600 c.c.) in an atmosphere of nitrogen which was maintained during all further methylations involving sodium hydroxide. The solution was cooled to 10° and dimethyl sulphate (270 c.c.) was added during 8 hr. with vigorous stirring, the temperature being kept below 15°. The mixture was set aside for 18 hr., after which the methylation was repeated twice. After cooling to 5° the solution was acidified by cautious addition of 50% sulphuric acid, and the mixture dialysed against running water for 24 hr. Concentration to 200 c.c. was followed by three methylations as before, acidification, and dialysis for 4 days. The pH was adjusted to 2 with sulphuric acid and a further equal volume of acid added. Dialysis (until the solution was free from sulphate ions) and evaporation gave an amorphous solid (14·0 g.) (Found: ash, 5·0; OMe, 28·4%). A portion (9·0 g.) of this material, dissolved in water, was de-ionised with Amberlite IR-120 $H^+$ resin and then stirred overnight with an 8—10-fold excess of silver carbonate. Filtration and freeze-drying gave an amorphous silver salt which was triturated with methyl iodide (50 ml.); the mixture was then refluxed with the addition of silver oxide (4 g.) in portions (0·5 g.). The product obtained on filtration and evaporation was methylated three times according to Purdie's directions. The fully methylated polysaccharide (6·2 g.) had $[\alpha]_D^{18}$ +68·4° (*c* 1·17 in $CHCl_3$) (Found: OMe, 42·3%).

*Hydrolysis of the Methylated Polysaccharide.*—Methanolysis of the polysaccharide (6·0 g.) with 8% methanolic hydrogen chloride (150 c.c.) at 100° in a sealed tube for 18 hr. was followed by hydrolysis with 4% hydrochloric acid for 6 hr. at 100°. Neutralisation with silver carbonate

[19] Hamilton, Spriestersbach, and Smith, *J. Amer. Chem. Soc.*, 1957, **79**, 443.
[20] Ehrlich, *Ber.*, 1932, **65**, 352.

and removal of silver ions with hydrogen sulphide gave a solution which was made alkaline with barium hydroxide, excess of alkali being then removed by passage of carbon dioxide through the solution. A viscous syrup (5·73 g.) was isolated from which the neutral methylated sugars were extracted by refluxing dry diethyl ether (4 × 100 c.c.). Removal of the ether gave a syrup (1·54 g.). The residual barium salts (4·0 g.) were further hydrolysed with 2N-sulphuric acid at 100° for 21 hr. A brown amorphous solid was obtained which gave a further quantity of neutral sugars (0·20 g.) on extraction with dry ether. The residue (2·10 g.) consisted of methylated barium uronates.

*Fractionation of the Neutral Methylated Sugars.*—The methylated sugars (1·74 g.) were partitioned on a cellulose column (850 × 30 cm.), eluted with butan-1-ol–light petroleum (b. p. 100—120°) (30 : 70; v/v) saturated with water. After the collection of 2·3 l. the proportions in the eluant were changed to (60 : 40; v/v) and after 12 l. had been collected the eluant was changed to water. Fractions were as follows, $R_G$ values being for solvent (3):

Fraction G (1·768—1·92 l.): Syrupy 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (0·127 g.), $R_G$ 0·88, $[\alpha]_D$ +113° (*c* 1·14) (Found: OMe, 51·9. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). The derived anilide had m. p. 190—191°, $[\alpha]_D^{18}$ −69° ⟶ +35° (*c* 0·75 in acetone).

Fraction H (1·928—2·230 l.): A syrup (0·307 g.), $R_G$ 0·86. Electroionophoresis showed two components of $M_G$ 0·36 and 0·0 respectively. Separation was achieved by partition on a column of "Celite 535" (50 × 3·0 cm.) developed with solvent (6). The syrup (0·305 g.), dissolved in the organic phase of solvent (6) (3 ml.), was absorbed on dry Celite (3 g.), and the mixture was packed on top of the column, giving:

Fraction (i) (775 c.c.—1025 c.c.), syrupy 2 : 3 : 4 : 6-tetra-*O*-methylgalactose (0·214 g.), $R_G$ 0·88, $[\alpha]_D^{18}$ +112° (*c* 2·1) (Found: OMe, 52·0%).

Fraction (ii) (1275—1300 c.c.), crystalline 3 : 4-di-*O*-methyl-L-rhamnose (0·036 g.), $R_G$ 0·85, $M_G$ 0·36, m. p. 93—94° $[\alpha]_D^{18}$ +23° (*c* 2·3) (Found: OMe, 32·9. Calc. for $C_8H_{16}O_5$: OMe, 32·3%) [demethylation gave rhamnose (paper chromatography)].

Fraction J (4·96—6·84 l.): Syrupy 2 : 3 : 6-tri-*O*-methyl-D-galactose (0·436 g.), $R_G$ 0·71, $[\alpha]_D^{20}$ +96° (*c* 1·8) (Found: OMe, 40·9. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). The derived lactone had m. p. 97—99°, $[\alpha]_D^{18}$ −40° ⟶ −30° (*c* 1·2) (constant), and gave one component on chromatography in solvents (4) or (5) (detected by spraying with alkaline hydroxylamine hydrochloride, then ferric chloride [21]).

Fraction K (10·8—11·84 l.): Crystalline 3-*O*-methyl-L-rhamnose (0·140 g.), $R_G$ 0·56, m. p. and mixed m. p. 114—115°, $[\alpha]_D$ +30° (*c* 1·0) (Found: OMe, 17·0. Calc. for $C_7H_{14}O_5$: OMe, 17·4%). The *X*-ray powder photograph was identical with that of the authentic material and distinct from that of 4-*O*-methyl-L-rhamnose. The derived lactone had $[\alpha]_D^{15}$ −20° (*c* 1·0).

Fraction L: Water-washings; methylated barium uronates (0·24 g.).

*Examination of the Methylated Barium Uronates.*—The combined methylated barium uronates (2·34 g.) were converted into the free uronic acids (1·70 g.) by treatment with Amberlite IR-120 $H^+$ resin. Partition on "Celite" as for fraction H with butan-1-ol–*n*-butyl acetate–acetic acid–water (50 : 6 : 4 : 40) as eluant gave three fractions:

(*a*) Fraction U 1 (0·35—0·65 l.): A syrup (1·0 g.), $[\alpha]_D$ +59° (*c* 0·93). Paper chromatography showed a single spot (solvent 4) identical with that of 2 : 3 : 4-tri-*O*-methylglucuronic acid, but development of a paper chromatogram with solvent 7 revealed two spots. Conversion of a portion into the methyl ester glycoside by treatment with 3% methanolic hydrogen chloride was followed by dissolution in dry tetrahydrofuran (5 c.c.) and reduction by the dropwise addition of a saturated solution of lithium aluminium hydride in dry tetrahydrofuran. The solution was refluxed gently for 30 min., then cooled and the excess of hydride was destroyed by ethyl acetate. Addition of water, evaporation to dryness, extraction of the residues with boiling acetone, then with dry chloroform, and evaporation of the extracts gave a syrup. Hydrolysis with N-hydrochloric acid (5 c.c.) at 100° for 6 hr. gave a syrup (0·279 g.) which was partitioned on a cellulose column (25 × 42 cm.) with solvent 7. Solvent was removed from the respective fractions at 30—40° in a stream of nitrogen.

Fraction M (0·054 g.) was purified by separation on Whatman 3MM paper with solvent 7. A syrup (0·028 g.) was isolated which had $R_G$ 0·88 (solvent 3), $R_F$ 0·83 (solvent 7), $M_G$ 0·36, $[\alpha]_D$ +17° (*c* 0·36) (Found: OMe, 29·5. Calc. for $C_8H_{16}O_5$: OMe, 32·3%). Demethylation of a portion of the syrup gave rhamnose (paper chromatography). The syrup was oxidised in aqueous solution with potassium periodate.[9]

[21] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.

Fraction *N*: A syrupy mixture (0·137 g.) of fractions M and P (paper chromatography, solvent 7).

Fraction *P*: 2 : 3 : 4-Tri-*O*-methyl-D glucose (0·062 g.), $[\alpha]_D$ +65° (*c* 0·18),[22] $R_G$ 0·85 (solvent 3), $R_F$ 0·72 (solvent 7), $M_G$ 0·0 (Found: OMe, 41·3. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). The derived *N*-phenyl-D-glucosylamine had m. p. and mixed m. p. with 2 : 3 : 4-tri-*O*-methyl-*N*-phenyl-D-glucosylamine 145—146°.[22]

(*b*) Fraction U 2 (0·85—1·6 l.) (0·239 g.): This fraction was contaminated with neutral sugars from which it was separated by elution on Whatman 3MM paper with solvent 7. The uronic acid remained on the starting line and was eluted with water, de-ionised (Amberlite IR-120 $H^+$), and evaporated to a syrup (0·083 g.) which had $[\alpha]_D$ +80° (*c* 0·33). A portion (0·060 g.) was converted into the ester glycoside, reduced, and hydrolysed as before. Chromatography (solvent 3) showed 2 : 3 : 4-tri-*O*-methyl-D-glucose $R_G$ 0·85, 3-*O*-methyl-L-rhamnose $R_G$ 0·56, rhamnose $R_G$ 0·28, and a mono-*O*-methylhexose $R_G$ 0·23. The material of $R_G$ 0·85 was separated on Whatman 3MM paper and examined electroionophoretically: a single spot of $M_G$ 0·0 was detected.

(*c*) Fraction U 3 (1·625—2 l.) (0·10 g.) had $[\alpha]_D^{20}$ +93° (*c* 0·38). Treatment as for the previous fraction gave a syrup containing six components (paper chromatography, solvents 3 and 7). These included the four sugars present in the previous fraction, together with 2 : 3 : 6-tri-*O*-methyl-D-galactose $R_G$ 0·71 and a di-*O*-methylhexose $R_G$ 0·46.

*Reduction and Remethylation of the Methylated Polysaccharide.*—The methylated gum (OMe, 42·3%) (0·75 g.) in dry tetrahydrofuran (1·5 c.c.) was reduced with lithium aluminium hydride as for fraction U 1. The solid product (0·61 g.) had $[\alpha]_D$ +75° (*c* 1·03 in $CHCl_3$). This material (0·41 g.) after four methylations with Purdie reagents had $[\alpha]_D$ +45·8° (*c* 2·6 in $CHCl_3$) (Found: OMe, 41·8%). Methanolysis with 4% methanolic hydrogen chloride for 8 hr. under reflux, followed by hydrolysis with N-hydrochloric acid for 16 hr. at 100°, gave a syrup (0·238 g.). Chromatography (solvents 3 and 7) showed all the components of fraction U 2 except the 2 : 3 : 4-tri-*O*-methylglucose and in addition 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose $R_G$ 1·0, 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose and 3 : 4-di-*O*-methylrhamnose $R_G$ 0·85. Tetramethylgalactose has $R_F$ 0·92 in solvent 7.

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[22] Peat, Schlucterer, and Stacey, *J.*, 1939, 581.

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## 395. *The Optical Stability of* (+)-*Methyl* 9-*Aminofluorene*-2-*carboxylate.*

By ALWYN G. DAVIES, E. E. EDWIN, and J. KENYON.

(+)-Methyl 9-aminofluorene-2-carboxylate is not optically unstable *per se*. Loss in rotatory power which it suffers on storage is due to chemical changes initiated by aerial oxidation. Recrystallisation restores the original rotatory power, provided that decomposition has not gone too far.

AFTER their experiments on the resolution of 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine Pope and Harvey [1] reported that this base racemises during liberation from its salts or during preparation of its derivatives. On the other hand it was shown by Pickard and Kenyon [2] that 1 : 2 : 3 : 4-tetrahydro-2-naphthol is optically stable. The present authors [3] re-examined the resolution of 1 : 2 : 3 : 4-tetrahydro-2-naphthylamine and showed that Pope and Harvey's conclusion of optical instability was explicable by the incompleteness of their resolution combined with differences of solubility between the (+)- and the (±)-compound with which they worked.

[1] Pope and Harvey, *J.*, 1901, **79**, 74.
[2] Pickard and Kenyon, *J.*, 1912, **101**, 1427.
[3] Davies, Edwin, and Kenyon, *J.*, 1956, 250.

Recently Ray and Kreiser [4] showed that, whilst (+)-9-hydroxyfluorene-2-carboxylic acid gave no evidence of optical instability, the corresponding (+)-methyl 9-aminofluorene-2-carboxylate " racemised readily, even on standing at room temperature, and recrystallisation was impossible without loss of activity." We repeated Ray and Kreiser's experiments and obtained (+)-methyl 9-aminofluorene-2-carboxylate with a rotatory power much more than that recorded by these authors. The (+)-base, when kept in the dark and in an atmosphere of nitrogen, maintains its rotatory power almost unimpaired for at least three weeks, and it can be recrystallised unchanged in melting point or optical activity. On the other hand, [α] falls to half its original value when the (+)-base in ethanolic solution in the presence of air is kept in the dark for 12 days; later, the solution became too yellow to permit its further measurement. When not protected from light the solutions are even more unstable: optical activity was fully maintained for at least 14 hr., but after 40 hr. had fallen by 25%. During 3 weeks the solution became deep green and deposited colourless crystals and evolved ammonia. In contrast (+)-methyl 9-acetamidofluorene-2-carboxylate which is chemically stable is also optically stable.

It appears then that the free base is not optically unstable *per se*, and that loss of rotatory power results from chemical reaction with air.

It was shown by Goldschmidt *et al.*[5] that 9-aminofluorene is readily oxidised in air to coloured solutions which evolve ammonia and deposit almost colourless, sparingly soluble tetra-9-fluorenylhydrazine. Diphenylmethylamine on the other hand gave diphenylmethylenediphenylamine. The analysis of our product would be compatible with a structure analogous to either of these.

## Experimental

By following Ray and Kreiser's procedure [4] the hydrochloride of methyl 9-aminofluorene-2-carboxylate was obtained in excellent yield, with m. p. 238° (previous sintering). The free base separates from light petroleum in needles, m. p. 92—95°.

(+)-*Methyl* 9-*Aminofluorene*-2-*carboxylate*.—The hydrochloride of the (±)-base (12 g.) was thoroughly triturated with 3% sodium hydroxide solution (100 c.c.), and the liberated base washed thoroughly with water (a small portion, dried *in vacuo*, had m. p. 98—100°). The damp cake was suspended in a solution of (+)-tartaric acid (7 g.) in water (100 c.c.), and the whole gently heated until dissolution was complete. The crystals which separated overnight (crop A) were removed by filtration and roughly dried [needles, 12 g., m. p. 195° (Found: C, 55·6; H, 5·7; N, 3·4. Calc. for $C_{15}H_{13}O_2N,H_2O$: C, 56·0; H, 5·2; N, 3·4%)]. After recrystallisation from ethanol the salt had m. p. 210° and, as shown by analysis, was anhydrous (Found: C, 58·3; H, 4·8. Calc. for $C_{15}H_{13}O_2N$: C, 58·6; H, 4·9%).

The salt (A) was then recrystallised six times from water, previous experiments having shown this to be more than adequate for complete separation of the diastereoisomers, and a seventh time from ethanol to render the salt anhydrous. This least soluble fraction (1 g.) had m. p. 210° and $[\alpha]_D^{20}$ +41° (*l* 1; *c* 0·591 in $H_2O$).

Decomposition of this salt with aqueous sodium hydroxide yielded the free (+)-base (0·6 g.), m. p. 108—110°, $[\alpha]_D^{20}$ +52° (*l* 1; *c* 0·730 in EtOH). Recrystallisation did not alter the m. p. or [α] of the (+)-base.

*Experiments to show the Optical Stability and the Chemical Instability of* (+)-*Methyl* 9-*Aminofluorene*-2-*Carboxylate*.—(i) (+)-Methyl 9-aminofluorene-2-carboxylate, m. p. 100—103°, $[\alpha]_D^{20}$ +38° (*l* 1; *c* 0·580 in EtOH) (Found: C, 75·5; H, 5·6; N, 6·1. Calc. for $C_{15}H_{13}O_2N$: C, 75·3; H, 5·5; N, 5·85%), after 3 weeks in the dark in an atmosphere of nitrogen had $[\alpha]_D^{20}$ +37° (*l* 1; *c* 0·625 in EtOH).

(ii) A solution of the base, m. p. 105—108°, $[\alpha]_D^{20}$ +32° (*l* 1; *c* 0·713 in EtOH), in warm light petroleum was allowed to crystallise and the solvent then completely removed *in vacuo*. The crystals still had m. p. 105—108° and $[\alpha]_D^{20}$ +32·3° (*l* 1; *c* 0·715 in EtOH). After storage in the dark under nitrogen they had m. p. 105—108°, $[\alpha]_D^{20}$ +31·7° (*l* 1; *c* 0·835 in EtOH) and still gave excellent analytical values for C, H, and N.

[4] Ray and Kreiser, *J. Amer. Chem. Soc.*, 1945, **67**, 504; 1947, **69**, 3068.
[5] Goldschmidt *et al.*, *Annalen*, 1926, **447**, 197; 1927, **456**, 152.

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(iii) A solution of the base, m. p. 108—110°, $[\alpha]_D^{20}$ +52° (*l* 1; *c* 0·730 in EtOH), in ethanol, after 5 days under air in the dark had become slightly yellow and $\alpha_D^{20}$ +0·38° had fallen to $\alpha_D^{20}$ +0·25°. After 7 days more the solution had become distinctly yellow and had $\alpha_D^{20}$ +0·19°. Thereafter the solution became more deeply coloured and further measurements were impracticable.

(iv) A solution of the base, $[\alpha]_D^{20}$ +45° (*l* 1; *c* 0·972 in EtOH), in ethanol ($\alpha_D^{20}$ +0·44°) was kept under air but not protected from daylight. After 14 hr. the rotation was unchanged, but after 40 hr. had fallen to $\alpha_D^{20}$ +0·32° and the solution had become slightly yellow. During the next 4—5 days the colour gradually became deep green and colourless needles began to separate: concurrently the solution gradually lost some of its own colour. After being washed with ethanol this *substance* had m. p. 165°, unchanged after recrystallisation from ethanol (Found: C, 78·6; H, 4·6; N, 2·3. $C_{30}H_{21}O_4N$ requires C, 78·4; H, 4·6; N, 3·0. $C_{60}H_{44}O_8N_2$ requires C, 78·2; H, 4·8; N, 3·0%).

(v) A solution of the (±)-base, m. p. 93—95° [freshly liberated from its (stable) hydrochloride and dried] (1 g.), in ethanol (10 c.c.) was kept for 3 weeks: it became deep green and deposited colourless needles. There was a strong smell of ammonia on opening the flask; the crystals (*ca.* 0·7 g.) separated from ethanol in needles, m. p. 165°, unchanged on recrystallisation (Found: C, 78·55; H, 4·6; N, 2·3%).

*Optical and Chemical Stability of* (+)-*Methyl* 9-*Acetamidofluorene*-2-*carboxylate*.—By interaction with acetic anhydride and pyridine the base (0·5 g.) of $[\alpha]_D^{20}$ +32° was quantitatively converted at room temperature into (+)-*methyl* 9-*acetamidofluorene*-2-*carboxylate*, needles (0·4 g.) (from ethanol), m. p. 246°, $[\alpha]_D^{20}$ +26° (*l* 1; *c* 0·862 in EtOH) (Found: C, 72·8; H, 5·0; N, 5·2. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·4; N, 5·0%). The solution in ethanol retained its rotatory power undiminished for a week and the crystalline acetyl derivative, after 2 weeks in a vessel exposed to air and light, had $[\alpha]_D^{20}$ +26·2° (*l* 1; *c* 0·930 in EtOH).

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## 396. *The Chemistry of Nitryl Chloride. Part III.*[1] *The Reaction with Naphthalene, Anisole, Phenol, and* p-*Diethoxybenzene.*

By M. J. COLLIS and D. R. GODDARD.

The extent of the chlorination and nitration of naphthalene, anisole, phenol, and *p*-diethoxybenzene by nitryl chloride dissolved in an inert solvent has been measured. The principal reaction with anisole is chlorination and with phenol nitration. In the case of naphthalene and *p*-diethoxybenzene the two reactions proceed simultaneously.

IT has been reported[1] that nitryl chloride chlorinates alkylbenzenes, the extent of nitration being almost negligible. On the other hand, Steinkopf and Kuhnel[2] found that only *o*-nitrophenol was formed when nitryl chloride interacted with phenol at low temperature, although at room temperature 2 : 4-dichloro-6-nitrophenol was obtained. Naphthalene was simultaneously chlorinated and nitrated, to give α-nitro- and α-chloronaphthalene. With anisole, they obtained a colourless easily decomposable product which appeared to be an addition compound: on decomposition, it evolved chlorine and nitrogen dioxide, leaving anisole. Price and Sears[3] studied the reactions of nitryl chloride with various aromatic compounds in the presence of Lewis acids such as aluminium

[1] Part II, Gintz, Goddard, and Collis, *J.*, 1958, 445.
[2] Steinkopf and Kuhnel, *Ber.*, 1942, **75**, 1323.
[3] Price and Sears, *J. Amer. Chem. Soc.*, 1953, **75**, 3276.

trichloride. They found that anisole, naphthalene, and phenol tended to undergo oxidative degradation; in the case of naphthalene they obtained a 31% yield of α-nitronaphthalene but with anisole and phenol they were only able to isolate traces of nitrocompounds. They found no evidence for chlorination.

The object of the present work was to study more closely the relative importance of chlorination and nitration, in the reaction of nitryl chloride with these more reactive aromatic nuclei. The results, which are tabulated, show that with anisole chlorination

| Compound | Temp. | $NO_2Cl$ (mole/l.) | ArH : $NO_2Cl$ | Solvent | Chlorination (% based on initial $NO_2Cl$) | Nitration (% based on initial $NO_2Cl$) |
|---|---|---|---|---|---|---|
| Naphthalene ... | 20° | 0·22 | 3 : 1 | $CH_2Cl_2$ | 62% in 2½ hr. | 62% in 1½ hr. |
| Anisole ..... | −20 | 1·9 | 1 : 1 | ,, | 24% in 1 hr. | 0% in 1 hr. |
| ,, ..... | ,, | ,, | ,, | ,, | 46% in 1¾ hr. | 43% in 1¾ hr. |
| ,, ..... | +5 | 1·7 | 1 : 1 | $C_6H_6$ | 50% in 1½ hr. | 56% in 1½ hr. |
| ,, ..... | +10 | 0·24 | 3 : 1 | ,, | 35% in 1 hr. | 0% in 1 hr. |
| Phenol ..... | −60 | 0·13 | 3 : 1 | $CH_2Cl_2$ | 14% in ½ hr. | 62% in ½ hr. |
| *p*-$C_6H_4(OEt)_2$ ... | −80 | 0·13 | 1 : 1 | ,, | 39% in ½ hr. | 41% in ½ hr. |
| ,, ... | +20 | 0·12 | 3 : 1 | ,, | 58% in 1 hr. | 69% in 1 hr. |

*Products of reaction with nitryl chloride.*

| Compound | Temp. | $NO_2Cl$ (mole/l.) | ArH : $NO_2Cl$ | Solvent | Reaction time | Products (and yields *) |
|---|---|---|---|---|---|---|
| Naphthalene | 20° | 1·2 | 2 : 1 | $CH_2Cl_2$ | 1 hr. | 1-Nitronaphthalene (45%) |
| Anisole ..... | −20 | 1·9 | 1 : 1 | ,, | 1¾ hr. | Chloroanisoles (38%) |
| ,, ..... | +5 | 1·7 | 1 : 1 | $C_6H_6$ | 1½ hr. | ,, (23%) |
| Phenol ..... | −80 | 1·36 | 1 : 1 | $CH_2Cl_2$ | ½ hr. | *p*-Nitrophenol (22%) |
| | −50° to +20° | 0·52 | 1 : 2 | ,, | ¼ hr. | 2 : 4-Dichloro-6-nitrophenol (15%)<br>3 : 6-Dichloro-2-nitrophenol (5%) |
| *p*-$C_6H_4(OEt)_2$ | −80 | 1·0 | 1 : 1 | ,, | ½ hr. | 1 : 4-Diethoxy-2-nitrobenzene (39%)<br>2-Chloro-1 : 4-diethoxybenzene (4%) |

* Yields were based on the component in limited quantity, generally nitryl chloride.

precedes nitration, and it is likely that nitration is due to nitrous acid formed in the chlorination. With naphthalene and *p*-diethoxybenzene the two reactions are simultaneous, and with phenol at low temperature nitration predominated. Lowering the temperature in the case of naphthalene reduced nitration and chlorination equally. A lower temperature could not be conveniently employed with *p*-diethoxybenzene since even at −80° both reactions were very rapid.

These results do not enable one to draw definite conclusions regarding the chlorinating and nitrating properties of nitryl chloride, but they indicate that nitryl chloride is less reactive as a nitrating than as a chlorinating agent. Thus, with the less reactive aromatic nuclei chlorination predominates, and with the more reactive compounds the inherent reactivity of the reagent is of less importance and nitration predominates. This principle is illustrated by the fact that toluene is brominated only 20 times faster than benzene by the more reactive agent $Br^+$ but 400 times faster by the less reactive agent $Br_2$.[4]

The orientation of one of the products (3 : 6-dichloro-2-nitrophenol) isolated when phenol was treated with an excess of nitryl chloride is very strange. We know of no explanation of this.

## Experimental

*Determination of the Extent of Chlorination and Nitration.*—Portions of the reaction mixtures were withdrawn and hydrolysed, and the total acid and chloride were titrated. The amount of chlorination was obtained from the reduction in ionisable chlorine content and that of nitration by the reduction in the nitric or nitrous acid. When phenol was used, the total acid had to be determined potentiometrically owing to the colour of the nitrophenol.

*Isolation of Products.—Anisole.* 0·23 mole of anisole was added to 100 c.c. of a 2·3M-solution of nitryl chloride in methylene chloride cooled to −20°. After 1¾ hr., the mixture was poured

[4] Robertson, *Sci. Progr.*, 1955, **43**, 418.

into water and the organic layer separated and washed with sodium hydrogen carbonate solution. The washings were red, owing presumably to the presence of nitrophenols which have previously been noted as being formed in the nitration of anisole.[5] After being dried, the organic layer was evaporated at room temperature and 30 mm. The residue was fractionally distilled through a helix column at 10 mm. Excess of anisole distilled first, then the main fraction (10 c.c.), b. p. 74—75°/10 mm., a mixture of chloroanisoles. The small residue of yellow liquid did not distil at constant temperature and was assumed to be a mixture of nitroanisoles. The chloroanisole fraction was refractionated, to give 4·5 c.c., b. p. 75°/10 mm., 195°/740 mm. (lit., *p*-chloroanisole, b. p. 198°; *o*-chloroanisole, b. p. 195°) (Found: C, 59·0; H, 5·1; Cl, 24·8. Calc. for $C_7H_7OCl$: C, 59·0; H, 5·0; Cl, 24·9%).

Nitrated with fuming nitric acid, this product give pale yellow crystals, m. p. 96—98° (4-chloro-2-nitroanisole has m. p. 98°, 2-chloro-4-nitroanisole, m. p. 95°).

In a similar experiment with benzene as solvent, the mixture was kept at +5° for 1¾ hr. It developed an intense violet colour similar to that noted in the nitration of anisole.[5] The reaction was stopped by addition of methyl alcohol. The solvent and methyl alcohol were distilled off at 30 mm. The distillate separated into two layers, the lower of which contained 12% of chlorine, showing that it probably contained chloroanisole which had distilled as a constant-boiling mixture. On fractionation of the residue chloroanisole was isolated as before but in lower yield (23%).

*Naphthalene.* Naphthalene (0·22 mole) was added to a 1·22M-solution (90 c.c.) of nitryl chloride in methylene chloride at room temperature. In a short while an exothermic reaction set in which caused the mixture to boil with loss of some material. After 1 hr. the mixture was poured into sodium hydrogen carbonate solution and the organic layer washed with water and then dried. The solvent was distilled off, and the mixture chromatographed on alumina. Two products were separated, one being unchanged naphthalene and the other 1-nitronaphthalene (3·1 g.). Both were contaminated with a chloro-compound, presumably chloronaphthalene which could not be separated. The 1-nitronaphthalene, purified by recrystallisation from aqueous alcohol, had m. p. 58° (Found: C, 68·9; H, 4·1; N, 8·2. Calc. for $C_{10}H_7O_2N$: C, 69·4; H, 4·1; N, 8·1%).

*Phenol.* Phenol (0·11 mole) was added to a 1·36M-solution (80 c.c.) of nitryl chloride in methylene chloride at −80°. The mixture was shaken but did not become completely homogeneous. After ½ hr. it was poured into 2M-sodium carbonate (100 c.c.) and the organic layer washed several times with a solution M in sodium carbonate and M in sodium hydrogen carbonate. The aqueous portions which were assumed to contain the nitrophenol were acidified, nitrite destroyed by the addition of sulphamic acid, and the whole steam-distilled. The initial distillate was yellow but only a small amount of what was assumed to be *o*-nitrophenol separated as a semi-solid. The residue was extracted with ether, and the ether layers were re-extracted with 2N-sodium hydroxide. On evaporation yellow crystals of sodium *p*-nitrophenoxide (4 g.) separated from the alkaline solution. The sodium salt was recrystallised several times from dilute sodium hydroxide and then converted into *p*-nitrophenol, m. p. 111—113° (Found: C, 52·6; H, 3·9; N, 10·2. Calc. for $C_6H_5O_3N$: C, 51·8; H, 3·6; N, 10·1%) (benzoate, m. p. 143°) [yield (based on impure sodium salt), 22%].

In another experiment, a 3M-solution (20 ml.) of phenol in methylene chloride was added to a 1·13M-solution (94 ml.) of nitryl chloride in the same solvent at −50°. The heat generated caused the temperature to rise rapidly despite cooling. In the working up, which was similar to that above, the nitrophenols were extracted with sodium hydrogen carbonate. On steam-distillation of the acidified extracts 3·3 g. of yellow solid were obtained. By fractional crystallisation from alcohol the solid was separated into 2 : 4-dichloro-6-nitrophenol (1·8 g. impure), m. p. 123—124° (lit., 122—123°) (Found: C, 34·8; H, 1·3; N, 6·5; Cl, 34·4. Calc. for $C_6H_3O_2NCl_2$: C, 34·6; H, 1·45; N, 6·7; Cl, 34·1%), and 3 : 6-dichloro-2-nitrophenol (0·6 g. impure), m. p. 70—72° (lit., 70°) (Found: C, 36·7; H, 1·6; N, 7·8; Cl, 32·2%).

p-*Diethoxybenzene.* *p*-Diethoxybenzene (0·11 mole) was added to a M-solution (100 c.c.) of nitryl chloride in methylene chloride at −80°. The mixture was well shaken but a large amount of solid remained undissolved. After ½ hr. it was poured into sodium carbonate solution. The organic layer was separated, dried, and evaporated. The residue, chromatographed on alumina, gave 1 : 4-diethoxy-2-nitrobenzene (7·7 g.), m. p. 49° (Found: C, 57·3; H, 6·0; N, 6·6. Calc for $C_{10}H_{13}O_4N$: C, 56·9; H, 6·2; N, 6·6%), and a white pasty solid which contained

[5] Bunton, Hughes, Ingold, Jacobs, Jones, Minkoff, and Reed, *J.*, 1950, 2628.

chlorine. The latter, assumed to be a mixture of chloro-*p*-diethoxybenzene with unchanged *p*-diethoxybenzene, was chromatographed again but the components were not completely separated.

In another experiment, with a slight excess of nitryl chloride (ratio $NO_2Cl$ : ArH 1 : 0·8), diethoxynitrobenzene was isolated as before (yield 43%) but the chlorodiethoxybenzene fraction was still not pure. However, on distillation of the latter a small quantity (0·8 g.) of pure 2-chloro-1 : 4-diethoxybenzene, b. p. 264—266°, was obtained (Found: C, 60·1; H, 6·6; Cl, 17·9. Calc. for $C_{10}H_{13}O_2Cl$: C, 59·8; H, 6·5; Cl, 17·7%).

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## 397. *The Chemistry of Nitryl Chloride. Part IV.* Addition to Styrene, Ethylene, and Propene.*

By D. R. Goddard.

Nitryl chloride with styrene forms 1 : 2-dichloro-1-phenylethane, with ethylene forms 1-chloro-2-nitroethane and 2-chloroethyl nitrite, and with propene forms 2-chloro-1-nitropropane and a small quantity of 2-chloro-1-methylethyl nitrite.

Nitryl chloride with olefins normally forms a chloro-nitro-adduct in which the nitro group is attached to the terminal position of the double bond irrespective of the electronic demands of substituents. Thus the direction of addition is the same in propene as in methyl acrylate. Shechter *et al.*[1] suggest that the mechanism involves homolysis of the nitryl chloride molecule. However, for the reactions of nitryl chloride with styrene in benzene Steinkopf and Kuhnel [2] reported the formation of 2-chloro-1-nitro-1-phenylethane in which the orientation is opposite to the usual one. In ether they obtained a *pseudo*-nitrosite. This work has been repeated and it has been found that nitryl chloride reacts with styrene both in benzene and in ether, to give 1 : 2-dichloro-1-phenylethane in 70—80% yield (based on the nitryl chloride). Another product, 1-chloro-2-nitro-1-phenylethane, was thought to be present, but could not be isolated: on distillation it decomposed, evolving hydrogen chloride, and ω-nitrostyrene was obtained though it was not present in the original reaction mixture.

Steinkopf and Kuhnel [2] report that nitryl chloride with ethylene gives only 1 : 2-dichloroethane. On the other hand, Petri [3] reports that 1-chloro-2-nitroethane (45% yield) and 2-chloroethyl nitrite (35% yield) are formed, and Ville and Dupont [4] confirmed the formation of 1-chloro-2-nitroethane (in 50% yield). The possible formation of a 2-chloroethyl nitrite was interesting in that it could be regarded as an indication of a mechanism involving heterolysis of nitryl chloride $^+Cl$–$NO_2^-$, the direction expected in view of the chlorinating properties of nitryl chloride. The present author found that nitryl chloride with ethylene in methylene chloride or benzene gave a product which decomposed, evolving oxides of nitrogen, on distillation. The presence of nitrite was suspected but unlike Petri (who gives no experimental details) the author was unable to isolate 2-chloroethyl nitrite. To avoid decomposition another sample of the product was mixed with

* Part III, preceding paper.

[1] Shechter, Conrad, Daulton, and Kaplan, *J. Amer. Chem. Soc.*, 1952, **74**, 3052.
[2] Steinkopf and Kuhnel, *Ber.*, 1942, **75**, 1323.
[3] Petri, *Z. anorg. Chem.*, 1948, **257**, 180.
[4] Ville and Dupont, *Bull. Soc. chim. France*, 1956, 804.

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methyl alcohol, to convert the nitrite into an alcohol, and on subsequent distillation 1-chloro-2-nitroethane (36% yield) and ethylene chlorohydrin (15% yield) were obtained.

After reaction of nitryl chloride with propene in ether, Price and Sears [5] isolated 2-chloro-1-nitropropane in 50% yield and a smaller quantity of *pseudo*nitrosite. Ville and Dupont,[4] using carbon tetrachloride and chloroform as solvents, obtained only 2-chloro-1-nitropropane in 40% yield. The author has re-investigated the reaction in order to see if a chloro-nitrito-product, similar to that obtained with ethylene, is formed, since an ionic addition mechanism would be expected to be more important in the case of a more reactive olefin. Methylene chloride and benzene were used as solvents (polar solvents dried by accepted methods could not be used owing to the hydrolysis of the nitryl chloride by the moisture that they contain [6]) and the reaction mixtures were treated immediately with an excess of methyl alcohol to convert any nitrite into an alcohol. On distillation 2-chloro-1-nitropropane was separated in 20—30% yield and, in low yield, impure 2-chloro-1-methylethyl alcohol. The total yield of products (based on the chlorine content) was low. Since very little residue was left after the distillation of the two compounds mentioned, the remaining product must have been evolved as a gas or have distilled with the solvent (see p. 1957). No dichloro-adduct could be detected.

The high proportion of dichloro-compound formed in the addition to styrene is difficult to explain, although it is interesting that a similar high proportion has been obtained with stilbene [2] and a smaller proportion with other olefins such as *cyclo*hexene.[5] The orientation of the chloro-nitro-compounds formed with styrene and propene is consistent with a mechanism involving homolysis of nitryl chloride, although heterolysis $NO_2^+ \cdots Cl^-$ cannot be excluded. The orientation of the chloro-nitrito-compound formed with propene supports the theory that such compounds are formed by a heterolysis $Cl^+ \cdots NO_2^-$.

## Experimental

Styrene was distilled under reduced pressure. Ethylene, supplied by British Oxygen Co., was 98·2% pure, the main impurity being nitrogen. Propene was prepared by passing *iso*propyl alcohol vapour over alumina pellets at 300—400°: the liquefied product was fractionally distilled (b. p. constant ±0·2°).

*Addition to Styrene.*—A 4·7M-solution (50 c.c.) of nitryl chloride in ether at −80° was added during *ca.* 1·5 hr. to 0·5 mole of styrene in ether at −80° (in Part I [6] it was shown that nitryl chloride and ether interact only above 0°). Reaction of the nitryl chloride was shown to be complete by hydrolysing a sample and titrating the total acid and the chloride (Mohr method). Ether was then removed at a water-pump and the excess of styrene at 2 mm. The residue was fractionally distilled through a 1-foot helix-packed column at 1 mm., giving: (*a*) 1 : 2-dichloro-1-phenylethane (15 c.c.), b. p. 67—69°/1 mm. (Found: Cl, 36·4%), giving on refractionation at 8 mm. 2 c.c., b. p. 99°/8, 232°/760 mm. (lit.,[7] b. p. 115°/15, and 233—234°/760 mm.) (Found: C, 55·0; H, 4·7; Cl, 40·2. Calc. for $C_8H_8Cl_2$: C, 54·9; H, 4·6; Cl, 40·5%); (*b*) ω-nitrostyrene (7 c.c.), b. p. 100—115°/1 mm., crystallising from aqueous alcohol as pale yellow needles, m. p. 57° (lit., 58°) (Found: C, 64·7; H, 4·9; N, 9·9. Calc. for $C_8H_7O_2N$: C, 64·6; H, 4·7; N, 9·4%), $\lambda_{max.}$ 310 mμ (in EtOH) (lit.,[8] 318 mμ in dilute HCl). Since the spectrum of the original reaction mixture (after removal of solvent) did not possess a maximum in this region and since hydrogen chloride was evolved continuously during the fractionation, it was concluded that the ω-nitrostyrene was formed by the decomposition of 1-chloro-2-nitro-1-phenylethane. In a similar experiment, instead of fractionally distilling the product it was chromatographed on alumina. 1 : 2-Dichloro-1-phenylethane was separated pure but the remainder was a brown oil of variable composition, owing presumably to decomposition by the alumina. Other chromatographic materials, *e.g.*, acid-washed alumina and silica, were tried without success.

In other experiments, benzene and methylene chloride were used as solvents. The products

[5] Price and Sears, *J. Amer. Chem. Soc.*, 1953, **75**, 3275.
[6] Collis, Gintz, Goddard, Hebdon, and Minkoff, *J.*, 1958, 438.
[7] Biltz, *Annalen*, 1897, **296**, 263.
[8] Kortum, *Z. phys. Chem.*, 1939, **43**, 271.

were separated chromatographically. Only 1 : 2-dichloro-1-phenylethane was obtained pure (yields: 74% in benzene; 67% in methylene chloride).

*Addition to Ethylene.*—Ethylene was slowly bubbled into a 1·75M-solution (100 c.c.) of nitryl chloride in methylene chloride at −5° to 0° and after 4 hr. reaction of the nitryl chloride was found to be complete. Methyl alcohol (50 c.c.) was added to convert any nitrite into alcohol, experience having shown that decomposition takes place if the mixture is distilled directly. After evaporation at atmospheric pressure, the residue was fractionally distilled at 32 mm.; the main fractions were: ethylene chlorohydrin (1·6 g.), b. p. 52—53°/32 mm., 125°/760 mm. (Found: C, 30·4; H, 7·0; Cl, 43·2. Calc. for $C_2H_5OCl$: C, 29·8; H, 6·3; Cl, 44·0%) (3 : 5-dinitrobenzoate, m. p. 94°; α-naphthylurethane, m. p. 100°), and 1-chloro-2-nitroethane (6·4 g.), b. p. 87—88°/32 mm., 173°/760 mm. (Found: C, 23·2; H, 3·85; N, 13·6; Cl, 31·5. Calc. for $C_2H_4O_2NCl$: C, 21·9; H, 3·7; N, 12·8; Cl, 32·4%) [gives *N*-2-nitroethylaniline hydrochloride, m. p. 104—106° (lit.,[4] m. p. 110°) (Found: Cl, 16·7. Calc. for $C_8H_{11}O_2N_2Cl$: Cl, 17·5%)]. Estimated yields (based on $NO_2Cl$) were ethylene chlorohydrin 16% and 1-chloro-2-nitroethane 35%. The same yields were obtained when benzene was used as solvent.

*Addition to Propene.*—A 5M-solution (85 c.c.) of nitryl chloride in benzene, at −5°, was added dropwise to benzene cooled to its f. p., through which propene (in a stream of nitrogen) was bubbled. When the reaction of the nitryl chloride was complete, 80 c.c. of absolute methyl alcohol were added. The methyl alcohol–benzene azeotrope was distilled off under reduced pressure and the residue fractionated, main fractions being impure 1-chloropropan-2-ol (4·2 g.), b. p. 46—50°/30 mm. (giving with dichromate a ketone whose 2 : 4-dinitrophenylhydrazone, m. p. 125°, did not depress the m. p. of chloroacetone 2 : 4-dinitrophenylhydrazone), and 2-chloro-1-nitropropane (9·3 g.), b. p. 64—65°/10 mm., 170—172°/760 mm. (lit.,[5] b. p. 172°) (Found: C, 29·5; H, 4·8; N, 11·1; Cl, 28·4. Calc. for $C_3H_6O_2NCl$: C, 29·2; H, 4·9; N, 11·3; Cl, 28·7) [giving *N*-(1-methyl-2-nitroethylaniline hydrochloride, m. p. 141° (Price and Sears [5] give m. p. 139—140°)]. Estimated yields (based on $NO_2Cl$) were 1-chloropropan-2-ol 5% and 2-chloro-1-nitropropane 30%. A number of minor fractions were obtained, some smelling of acetaldehyde, probably the result of oxidation of propene by the nitryl chloride. The benzene–methyl alcohol distillate (175 c.c.) contained 2·2% of organically combined chlorine because part of the product had formed a constant-boiling mixture with the solvent.

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Henry, *Bull. Acad. roy. Belg.*, 1897, **34**, 547.

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## 398. *Synthesis of Nucleoside-5′ Pyrophosphates.*

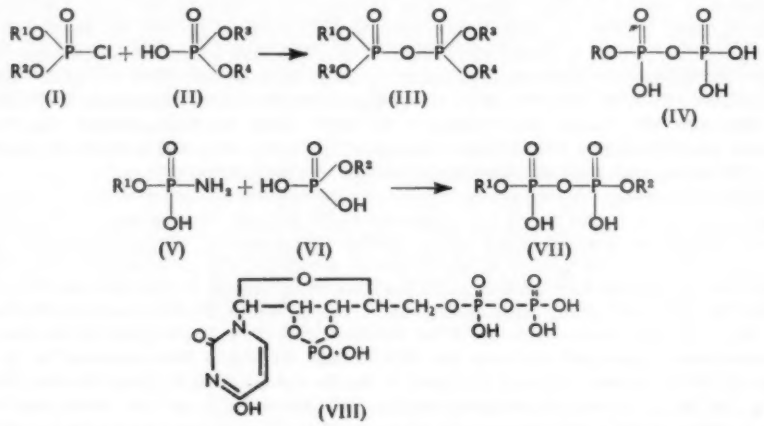
By A. M. Michelson.

Improved syntheses of uridine-5′ phosphate, cytidine-5′ phosphate, and uridine-2′(3′) : 5′ diphosphate are described. Adenosine-5′ pyrophosphate, uridine-5′ pyrophosphate, thymidine-5′ pyrophosphate, and uridine 2′ : 3′-(cyclic phosphate) 5′-pyrophosphate have been prepared in very high yield by treatment of the appropriate nucleotide with dibenzyl phosphorochloridate, followed by removal of benzyl groups. Uridine-5′ phosphate has been brominated to 5-bromouridine-5′ phosphate.

The biological importance of nucleoside-5′ pyrophosphates and triphosphates is now well established, both for their direct function in cellular metabolism and as components of various coenzymes. Methods for the synthesis of such nucleoside derivatives fall roughly into three groups: (*A*) Reaction of a phosphorochloridate with a phosphate, followed by removal of protecting groups. Examples of the variations of this method are the synthesis of adenosine-5′ pyrophosphate [1] (I + II; $R^1 = R^2 = R^3 =$ benzyl, $R^4 =$ nucleoside),

[1] Baddiley and Todd, *J.*, 1947, 648.

of uridine-5′ pyrophosphate [2] (I + II; $R^1 = R^3 = R^4$ = benzyl, $R^2$ = nucleoside), and of thymidine-5′ pyrophosphate and uridine-5′ pyrophosphate [3,4] (I + II; $R^1 = R^3$ = benzyl, $R^2$ = nucleoside, $R^4$ = H). (*B*) Treatment of the 5′-nucleotide with phosphoric acid and a suitable reagent such as di*cyclo*hexylcarbodi-imide [5] or *cyclo*pentanone oxime sulphonate.[6] (*C*) Reaction of phosphoramidates with phosphates; Todd and his co-workers [7] have thus synthesised adenosine-5′ pyrophosphate *via* (V; $R^1$ = benzyl) and




(VI; $R^2$ = nucleoside). The same compound has been prepared by Khorana and his colleagues [8] with the somewhat more useful nucleoside phosphoramidate (V; $R^1$ = nucleoside) and (VI; $R^2$ = H or benzyl). Treatment of a 5′-deoxy-5′-halogeno-nucleoside with a salt of tribenzyl pyrophosphate has also been used,[9,10] but owing to cyclisation [11] and other difficulties this method is of very limited application.

Use of method (*A*) requires protected nucleotide derivatives, usually involving a series of intermediates from the free nucleoside, while method (*B*) generally gives complex mixtures of phosphates, requiring tedious purification with low yields of the desired compound. Method (*C*) effected some improvement in both yield and specificity but, again, purification of the product by ion-exchange is desirable. Since an easy high-yielding synthesis of nucleoside-5′ pyrophosphates would be valuable, the classical method was re-investigated, by techniques not available at the time of the original syntheses of adenosine-5′ pyrophosphate [1] and triphosphate.[12,13] It was found that quantitative yields of nucleoside-5′ pyrophosphates (IV; R = nucleoside) were obtained by treating the unprotected 5′-mononucleotide (II; $R^3$ = nucleoside, $R^4$ = H) directly with dibenzyl phosphorochloridate [14] (I; $R^1 = R^2$ = benzyl) to give the $P^1$-nucleoside $P^2$-dibenzyl hydrogen pyrophosphate (III; $R^1 = R^2$ = benzyl, $R^3$ = nucleoside, $R^4$ = H) from which the benzyl groups were readily removed by catalytic hydrogenation. Under the conditions employed, triphosphate was not formed and the crude pyrophosphates were approximately

[1] Kenner, Todd, and Weymouth, *J.*, 1952, 3675.
[2] Griffin and Todd, *J.*, 1958, 1389.
[3] Michelson and Todd, *J.*, 1956, 3459.
[4] Khorana, *J. Amer. Chem. Soc.*, 1954, **76**, 3517.
[5] Chase, Kenner, Todd, and Webb, *J.*, 1956, 1371.
[6] Clark, Kirby, and Todd, *J.*, 1957, 1497.
[7] Chambers, Moffatt, and Khorana, *J. Amer. Chem. Soc.*, 1957, **79**, 4240.
[8] Anand, Clark, Hall, and Todd, *J.*, 1952, 3665.
[9] Michelson, unpublished work.
[10] Clark, Todd, and Zussman, *J.*, 1951, 2952.
[11] Baddiley, Michelson, and Todd, *J.*, 1949, 582.
[12] Michelson and Todd, *J.*, 1949, 2487.
[13] Atherton, Openshaw, and Todd, *J.*, 1945, 382.

95% pure and could be further purified by precipitation of the calcium salt from acid solution by the addition of ethanol. Purification by the elegant but somewhat tedious ion-exchange chromatography was not necessary, the synthetic compounds being homogeneous on paper chromatography, paper electrophoresis, and analytical ion-exchange chromatography and identical in such behaviour with authentic specimens. Thymidine-5′ and uridine-5′ pyrophosphate were hydrolysed by acid to the monophosphates only, under conditions in which the symmetrical di(nucleoside-5′) pyrophosphates are stable.

Uridine-5′ phosphate was prepared from 2′ : 3′-*O*-*iso*propylideneuridine [15] by a modification of the " polyphosphoric acid " method used by Hall and Khorana,[16] whereby the necessity for ion-exchange purification of the product was eliminated. The protected nucleoside was treated with a mixture of phosphoric acid and phosphoric oxide, and the resultant polyphosphates were hydrolysed. Treatment of the aqueous solution with baryta to pH 6·5 precipitated orthophosphate which was removed, and the uridine-5′ phosphate in the filtrate was isolated either as the barium salt or the free nucleotide in 70—80% yield. Traces of uridine and uridine-2′(3′) : 5′ diphosphate are satisfactorily removed by this process. A similar treatment of 2′ : 3′-*O*-benzylidenecytidine [17] gave crystalline cytidine-5′ phosphate in good yield.

A solution of anhydrous tri-*n*-octylammonium uridine-5′ hydrogen phosphate in dioxan was treated with dibenzyl phosphorochloridate (1·5—4 mols.) and tri-*n*-butylamine at room temperature for three hours. Paper chromatography showed complete conversion into $P^1$-uridine-5′ $P^2P^2$-dibenzyl hydrogen pyrophosphate (III; $R^1$ = uridine, $R^2$ = H, $R^3$ = $R^4$ = benzyl) which was precipitated from solution by ether. Hydrogenation in 70% ethanol was complete in 5—20 min. at a palladium catalyst, and the pyrophosphate (III; $R^1$ = uridine, $R^2$ = $R^3$ = $R^4$ = H) was isolated as its acid calcium salt in 90% yield. Analogous reactions with tri-*n*-octylammonium thymidine-5′ and adenosine-5′ hydrogen phosphate gave 80—90% yields of the corresponding pyrophosphates. In one preparation precipitation of the benzylated intermediate by ether was omitted; hydrogenation was then very slow owing to catalyst poisons and a good yield of $P^1$-adenosine-5′ $P^2$-benzyl dihydrogen pyrophosphate (VII; $R^1$ = adenosine, $R^2$ = benzyl) was obtained. When a mixture of uridine-2′ : 5′ diphosphate and uridine-3′ : 5′ diphosphate (prepared by an improvement of the " polyphosphoric acid " method [16] utilising the reverse temperature-solubility properties of the barium salts of such phosphates [18]) was treated with excess of dibenzyl phosphorochloridate, it gave after hydrogenolysis of the benzyl groups a good yield of uridine 2′ : 3′-(cyclic phosphate) 5′-pyrophosphate (VIII). Mild acid hydrolysis of this derivative broke both the cyclic phosphate and the pyrophosphate linkage to give the original mixture of uridine-2′(3′) : 5′ diphosphates. The compound is of some interest as a possible chain-terminating nucleotide in the enzymic synthesis of polynucleotides from pyrophosphates, described by Ochoa and his co-workers.[19] Its preparation serves to demonstrate the mildness of the method, which could readily be extended to the synthesis of such unstable derivatives as deoxyadenosine-5′ pyrophosphate, since at no time are strongly acidic conditions employed.

An alternative approach to pyrophosphate derivatives lies in the treatment of the mononucleotides with tetraesters of pyrophosphoric acid, utilising the well-known disproportionation reaction.[20] When uridine-5′ phosphate was treated with tetraphenyl pyrophosphate [21] at room temperature, quantitative formation of $P^1$-uridine-5′ $P^2P^2$-diphenyl hydrogen pyrophosphate (III; $R^1$ = uridine, $R^2$ = H, $R^3$ = $R^4$ = phenyl) was observed. At neutrality and room temperature this derivative was relatively stable, and did not

[15] Levene and Tipson, *J. Biol. Chem.*, 1934, **106**, 113.
[16] Hall and Khorana, *J. Amer. Chem. Soc.*, 1955, **77**, 1871.
[17] Gulland and Smith, *J.*, 1948, 1527.
[18] Dekker, Michelson, and Todd, *J.*, 1953, 947.
[19] Grunberg-Manago and Ochoa, *J. Amer. Chem. Soc.*, 1955, **77**, 3165.
[20] Corby, Kenner, and Todd, *J.*, 1952, 1234.
[21] Khorana and Todd, *J.*, 1953, 2257.

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give rise to diuridine pyrophosphate through further disproportionation. In view of the easy syntheses described above, this modification was not elaborated to preparative work.

Kenner, Todd, and Weymouth [22] reported the chlorination of 2′ : 3′-*O*-*iso*propylideneuridine to 5-chloro-2′ : 3′-*O*-*iso*propylideneuridine by *N*-chlorosuccinimide. When a dioxan solution of tri-*n*-octylammonium uridine-5′ hydrogen phosphate was treated with *N*-bromosuccinimide at room temperature for one week, 5-bromouridine-5′ phosphate (isolated as its calcium salt) was produced.

## Experimental

*Cytidine-5′ Phosphate.*—Anhydrous 2′ : 3′-*O*-benzylidenecytidine [17] (8 g.) was stirred into a solution of phosphoric oxide (15 g.) in 90% phosphoric acid (20 g.), and the mixture kept at 60° for 2 hr., under anhydrous conditions, with occasional stirring. Water (200 c.c.) was added and the solution placed on a boiling-water bath for 30 min. Aqueous barium hydroxide was then added to pH 6·5, and the hot solution filtered, the barium phosphate precipitate being washed well with hot water, and the filtrates evaporated to small volume under reduced pressure. The pH was adjusted to 7·1 with barium hydroxide, and two volumes of ethanol were added. The precipitated barium cytidine-5′ phosphate was washed with ethanol and ether and dried (7·0 g.). This product was dissolved in water (100 c.c.), and N-sulphuric acid (*ca.* 20 c.c.) was added to remove barium (rhodizonic acid used as indicator). The boiling solution was filtered through Hyflo Supercel and concentrated to *ca.* 30 c.c. under reduced pressure, and the hot solution was filtered. Boiling ethanol (*ca.* 100 c.c.) was added slowly and, after cooling, the deposited crystalline cytidine-5′ phosphate was collected (3·75 g.); it softened at 215°, decomposed at 232° (Found: N, 13·0; P, 9·7. Calc. for $C_9H_{14}O_8N_3P$: N, 13·0; P, 9·6%).

*Uridine-5′ Phosphate.*—A solution of 2′ : 3′-*O*-*iso*propylideneuridine [15] (2·75 g.) in 85% phosphoric acid (13 g.) and phosphoric oxide (10 g.) was kept at 60° for 2 hr. Water (100 c.c.) was then added and the mixture heated at 100° for ½ hr. Barium hydroxide solution was added to pH 6·5 and the boiling suspension (total vol. *ca.* 1 l.) filtered, the precipitated barium phosphates being well washed with hot water. The filtrates were taken to small volume (*ca.* 40 c.c.) under reduced pressure and adjusted to pH 7·4 with barium hydroxide solution, and two volumes of ethanol were added. The precipitated barium uridine-5′ phosphate was collected at a centrifuge, washed with ethanol and ether, and dried (3·41 g.). A solution of this salt in water (100 c.c.) was passed through a column of IR-120 ($H^+$ form; 2·5 × 6 cm.), and the eluate concentrated to small volume under reduced pressure. Ethanol and benzene were added and the residual water was removed by azeotropic distillation; the residue was dissolved in ethanol (15 c.c.) and filtered into dry ether (200 c.c.) with stirring. The precipitated uridine-5′ phosphate was collected, washed with ether, and dried, to a white powder (2·19 g., 70%) (Found, in material dried at 100°/$10^{-3}$ mm. for 6 hr.: N, 8·5; P, 9·7. Calc. for $C_9H_{13}O_9N_2P$: N, 8·6; P, 9·6%). A similar run from 7 g. of *iso*propylideneuridine gave 8·95 g. (80%) of the pure barium salt of uridine-5′ phosphate.[23]

*Uridine-5′ Pyrophosphate.*—Tri-*n*-octylamine (0·545 g., 1 mol.) was added to a solution of uridine-5′ phosphate (0·5 g.) in ethanol (10 c.c.), and the mixture evaporated to dryness under reduced pressure. The residual monotri-*n*-octylammonium uridine-5′ phosphate was a glass which was dried by evaporating its solution in dioxan, benzene, and toluene to dryness several times. To the product in dry dioxan (10 c.c.) and benzene (5 c.c.) was added dibenzyl phosphorochloridate [from 0·61 g. of dibenzyl phosphite and 0·315 g. of *N*-chlorosuccinimide in 10 c.c. of dioxan and 5 c.c. of benzene at room temperature (2 hr.)], followed immediately by tri-*n*-butylamine (0·428 g., 1·5 mol.) in dioxan (15 c.c.) and benzene (5 c.c.) dropwise during 10 min. The mixture was kept at room temperature for a further 3 hr., then solvent was removed under reduced pressure and the residue shaken with ether (50 c.c.) and *n*-heptane (50 c.c.). The gummy precipitate was hydrogenated in 70% ethanol (50 c.c.) at atmospheric temperature and pressure over palladium (PdO) and palladised–charcoal. Uptake was complete in 10 min. Catalyst was removed and the filtrate neutralised to pH 7·4 with triethylamine, then taken to small volume (*ca.* 10 c.c.), ethanol (50 c.c.) was added, and the solution filtered. To this filtrate

[22] Kenner, Todd, and Weymouth, *J.*, 1952, 3675.
[23] Michelson and Todd, *J.*, 1949, 2476.

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was added calcium chloride (0·75 g.) in 90% ethanol (10 c.c.). The precipitated calcium salt was collected by centrifugation, washed with ethanol and ether, and dried. Water (10 c.c.) was added to this salt, then N-hydrochloric acid to pH 3·6. The solution was filtered and ethanol (25 c.c.) added to the filtrate, to give calcium uridine-5′ pyrophosphate as a white powder, which was collected, washed with ethanol and ether, and dried (0·605 g.). Paper chromatography showed only traces of uridine-5′ phosphate and inorganic phosphate. A similar run with 4 mols. of dibenzyl phosphorochloridate and 0·5 g. of uridine-5′ phosphate gave 0·710 g. of a less pure calcium salt of uridine-5′ pyrophosphate. The two preparations were combined (1·315 g.) and water (10 c.c.) was added. The pH was adjusted to 4·2, and the solution clarified by centrifugation. Hydrochloric acid was then added to pH 2·5, followed by ethanol (30 c.c.). The precipitated calcium hydrogen uridine-5′ pyrophosphate was collected, washed with ethanol and ether, and dried (0·95 g.). Paper chromatography and electrophoresis showed that this product was homogeneous and contained only uridine-5′ pyrophosphate as organic constituent (Found, in material dried at 50°/$10^{-3}$ mm. for 12 hr.: N, 6·0; P, 14·2. Calc. for $C_9H_{13}O_{12}N_2P_2Ca$: N, 6·3; P, 14·0%).

*Thymidine-5′ Pyrophosphate.*—A solution of diammonium thymidylate dihydrate (0·5 g.) in water (100 c.c.) was passed through a column of IR-120 ($H^+$ form; 1 × 8 cm.) and the eluate evaporated to *ca.* 20 c.c. under reduced pressure. Tri-*n*-octylamine (0·45 g., 1 mol.) was then added, and the mixture evaporated to dryness several times with dioxan, benzene, and toluene to give the anhydrous tri-*n*-octylamine salt of thymidine-5′ phosphate as needles. To this in dry dioxan (10 c.c.) and anhydrous benzene (5 c.c.), dibenzyl phosphorochloridate (from 0·50 g. of dibenzyl phosphite, etc.) was added. Tri-*n*-butylamine (0·354 g., 1·5 mol.) in dioxan (10 c.c.) was then run in during 10 min. The mixture was kept at room temperature for a further 3 hr. and worked up as described for uridine-5′ pyrophosphate. Hydrogenation was complete in 20 min. The crude calcium salt obtained by addition of calcium chloride to an alcoholic solution of the amine salts was dissolved in water (10 c.c.) at pH 3·5 with hydrochloric acid, and after filtration ethanol (40 c.c.) was added. The precipitated calcium hydrogen thymidine-5′ pyrophosphate was washed with ethanol and ether and dried (0·515 g.). Spectroscopic and paper-chromatographic examination showed that this product was 92% pure on a weight basis, representing an actual yield of 85% of thymidine-5′ pyrophosphate. Traces of thymidine-5′ phosphate and inorganic phosphate were present. A similar run with 4 mols. of dibenzyl phosphorochloridate gave a 95% yield. The preparations (total 1·215 g.) were combined, dissolved in water (10 c.c.) at pH 4·2, and clarified by centrifugation, and to the supernatant liquid and washings were added 4 volumes of ethanol. The precipitated pure calcium hydrogen thymidine-5′ pyrophosphate was collected, washed with ethanol and ether, and dried (0·836 g.). Paper chromatography and electrophoresis showed that the compound was homogeneous and contained thymidine-5′ pyrophosphate as sole organic ingredient (Found, in material dried at 50°/$10^{-3}$ mm. for 12 hr.: N, 6·2; P, 14·0. $C_{10}H_{14}O_{11}N_2P_2Ca$ requires N, 6·4; P, 14·1%).

*Adenosine-5′ Pyrophosphate.*—Tri-*n*-decylamine (0·95 g., 1·5 mols.) was added to a suspension of adenosine-5′ phosphate (0·5 g.) in methanol (35 c.c.) and ethanol (35 c.c.), and the mixture boiled under reflux until a clear solution was obtained. Solvent was then removed under reduced pressure, and the residue dried in the usual manner and finally dissolved in anhydrous dioxan (10 c.c.). A solution of dibenzyl phosphorochloridate (from 0·567 g. of dibenzyl phosphite and 0·293 g. of *N*-chlorosuccinimide in 10 c.c. of dioxan at room temperature for 1 hr.) was added, followed dropwise by tri-*n*-butylamine (0·4 g., 1·5 mols.) in dioxan (5 c.c.). The mixture was kept at room temperature for a further 2 hr. with stirring, then evaporated to *ca.* 10 c.c. under reduced pressure, and stirring was continued for a further hour. Solvent was removed under reduced pressure and the residual syrup shaken vigorously with 1 : 1 ether–*n*-heptane (2 × 50 c.c.). The gummy precipitate was hydrogenated in 70% ethanol in the usual way, and worked up as for uridine-5′ pyrophosphate. The crude calcium salt was dissolved in N/25-hydrochloric acid, two volumes of ethanol were added, and the precipitated calcium hydrogen adenosine-5′ pyrophosphate was washed with alcohol and ether and dried (0·530 g., 80%) (Found, in material dried at 50°/$10^{-3}$ mm. for 12 hr.: N, 14·6; P, 13·1. Labile P : acid stable P, 1·01. Calc. for $C_{10}H_{13}O_{10}N_5P_2Ca$: N, 15·0; P, 13·3%).

*Uridine-2′(3′) : 5′-Diphosphate.*—Anhydrous uridine (1 g.) in phosphoric acid (6 g.) containing phosphoric oxide (4 g.) was kept at 60° for 2½ hr. Water (60 c.c.) was added, and the solution kept at 100° for 30 min., then the hot solution was neutralised to pH 9 with hot concentrated

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lithium hydroxide solution. After cooling, the lithium phosphate was removed, the filtrate and washings were run through a column of IR-120($H^+$ form), and the effluent was neutralised to pH 7·4 with barium hydroxide solution. The precipitate was removed by centrifugation and the supernatant liquid and washings were concentrated to small volume under reduced pressure, heated to boiling to complete precipitation of the diphosphate, and filtered hot (washing being with a little hot water), and the collected dibarium uridine-2′(3′) : 5′ diphosphate was dried (2·45 g.) (Found, in air-equilibriated material: N, 3·2; P, 7·9. Calc. for $C_9H_{10}O_{12}N_2P_2Ba_2,8H_2O$: N, 3·4; P, 7·6%).

*Bistrioctylamine Salt of Uridine-2′(3′) : 5′ Diphosphate.*—The dibarium salt (1·7 g.) was shaken in water (500 c.c.) till dissolved, then passed through a small column of IR-120($H^+$ form) to remove barium, and the eluate was evaporated to small volume under reduced pressure. Tri-*n*-octylamine (1·465 g., 2 mols.) and ethanol (50 c.c.) were then added and the solution was evaporated to dryness; the residue was evaporated with dioxan and dry toluene to remove traces of moisture and stored *in vacuo* over phosphoric oxide.

*Uridine (2′ : 3′-Cyclic Phosphate) 5′-Pyrophosphate.*—Dibenzyl phosphorochloridate (from 0·96 g. of dibenzyl phosphite in 5 c.c. of dioxan and 5 c.c. of benzene plus 0·54 g. of *N*-chlorosuccinimide at room temperature for 1 hr.) was added to a solution of the bistri-*n*-octylamine salt of uridine-2′(3′) : 5′ diphosphate (from 1 g. of the dibarium salt) in dioxan (5 c.c.) and benzene (5 c.c.). A solution of tri-*n*-butylamine (0·905 g., 4 mols.) in dioxan (3 c.c.) and benzene (3 c.c.) was then added dropwise and the clear solution kept at room temperature for 3 hr. Solvent was removed under reduced pressure and ether (40 c.c.) and *cyclo*hexane (60 c.c.) were added to the residue. The precipitated gum was washed by decantation, then hydrogenated in 70% ethanol (50 c.c.) (20 min.), and the product was worked up in the usual way, ethanolic calcium chloride (250 mg.) being used to afford the calcium salt. The crude product was dissolved in 0·05N-hydrochloric acid (6 c.c.), and clarified at a centrifuge, and 3 volumes of ethanol were added. The precipitated *calcium hydrogen uridine (2′ : 3′-cyclic phosphate) 5′-pyrophosphate* was washed with ethanol and ether and dried (0·465 g.) [Found, in material dried at 50°/$10^{-3}$ mm. for 12 hr.: N, 5·0; P, 17·7. $(C_9H_{10}O_{14}N_2P_3)_2Ca_3$ requires N, 5·3; P, 17·8%].

*Attempted Synthesis of Uridine-5′ Triphosphate from the Diphosphate.*—A solution of calcium uridine diphosphate (300 mg.) in water (10 c.c.) was passed through a column of IR-120 ($H^+$ form; 1 × 8 cm.), washing being with water. The eluate was treated with tri-*n*-octylamine (0·48 g., 2 mols.) and ethanol, and the anhydrous salt prepared in the usual way. A solution of dibenzyl phosphorochloridate (from 0·355 g. of dibenzyl phosphite as above) was added, followed by tri-*n*-butylamine (0·252 g., 2 mols.) in benzene (5 c.c.) and dioxan (10 c.c.), and the mixture kept at room temperature for 3 hr. Working up and hydrogenating gave an acid calcium salt (277 mg.) which streaked on paper chromatography and was shown by paper electrophoresis to contain little if any triphosphate. Acid hydrolysis (N-acid at 100° for 10 min.) gave largely uridine-5′ phosphate, though a small spot was observed near the origin on chromatography in ethanol–M-ammonium acetate (5 : 2).

*5-Bromouridine-5′ Phosphate.*—Tri-*n*-octylamine (0·267 g., 1 mol.) in ethanol (10 c.c.) was added to uridine-5′ phosphate (0·245 g., 1 mol.) and the mixture evaporated to dryness and dried as previously described. The residue was dissolved in anhydrous dioxan (20 c.c.), *N*-bromosuccinimide (540 mg., 4 mol.) added with shaking, and the mixture kept at room temperature for 1 week, with occasional shaking, in a stoppered flask. Solvent was then removed under reduced pressure, the residue dissolved in ethanol and neutralised to pH 8 with triethylamine, and excess of alcoholic calcium chloride added. The precipitated calcium salt was dried, dissolved in water (7 c.c.) at pH 8 (a small amount of N-hydrochloric acid was added to effect dissolution), and filtered. Two volumes of ethanol were added and the *calcium 5-bromouridine-5′ phosphate* collected by centrifugation, washed with ethanol and ether, and dried (0·251 g., 75%), $\lambda_{max.}$ 275 mμ in N/50-HCl, density ratios 280/260 mμ = 1·41, 260/250 mμ = 1·64 (Found, in material dried at 50°/$10^{-3}$ mm. for 12 hr.: N, 5·8; P, 6·9. $C_9H_{10}O_9N_2PBrCa$ requires N, 6·3; P, 7·0%).

*Paper Chromatography.*—$R_F$ values are as follows for ascending chromatograms on Whatman No. 1 paper, the solvent being 95% ethanol–M-ammonium acetate (5 : 2): Uridine 0·64. Uridine-5′ phosphate 0·20. Uridine-5′ pyrophosphate 0·09. Uridine-2′(3′) : 5′ diphosphate 0·04. Uridine-2′ : 3′ cyclic phosphate 0·59. Uridine 2′ : 3′-(cyclic phosphate) 5′-pyrophosphate 0·05. $P^1P^2$-Di(uridine-5′) pyrophosphate 0·27. $P^1$-Uridine-5′ $P^2P^2$-diphenyl pyrophosphate

0·83. Uridine 2′ : 3′-(cyclic phosphate) 5′-($P^2P^2$-dibenzyl pyrophosphate) 0·71. Thymidine-5′ phosphate 0·31. Thymidine-5′ pyrophosphate 0·18. Thymidine-3′ : 5′ diphosphate 0·05. Thymidine-3′ thymidine-5′ phosphate 0·65. Dithymidine dinucleotide 0·24. Adenosine 0·58. Adenosine-5′ phosphate 0·13. Adenosine-5′ pyrophosphate 0·05. Adenosine-2′(3′) : 5′ diphosphate 0·02. $P^1$-Adenosine-5′ $P^2P^2$-dibenzyl pyrophosphate 0·77. $P^1$-Adenosine-5′ $P^2P^2$-benzyl pyrophosphate 0·48.

*Paper Electrophoresis.*—Movement towards the anode is tabulated, for Whatman No. 1 paper, 30 cm. in length, with (I) M/50-$KH_2PO_4$, 750 v for 75 min.; (II) M/50-$Na_2HPO_4$, 600 v for 60 min.; (III) 0·05M-$H{\cdot}CO_2NH_4$ at pH 3·5, 400 v for 60 min.

| | Movement (cm.) | | |
|---|---|---|---|
| | I | II | III |
| Uridine-5′ phosphate | 9·9 | 10·0 | 7·1 |
| Uridine-5′ pyrophosphate | 11·8 | 10·0 | 8·2 |
| Uridine-2′(3′) : 5′ diphosphate | 12·2 | 12·2 | 8·5 |
| Uridine 2′ : 3′-(cyclic phosphate) 5′-pyrophosphate | 14·8 | 11·9 | 9·3 |
| Adenosine-5′ phosphate | 9·2 | 9·6 | 5·2 |
| Adenosine-5′ pyrophosphate | 11·3 | 9·8 | 6·4 |
| Adenosine-2′(3′) : 5′ diphosphate | 12·7 | 11·1 | 7·0 |

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## 399. *Phosphoramidic Halides: Phosphorylating Agents Derived from Morpholine.*

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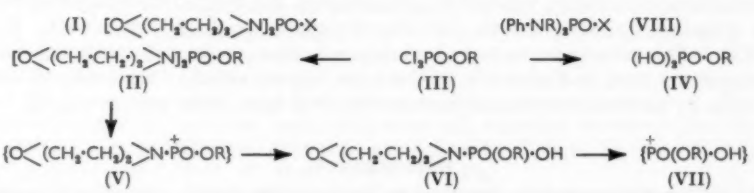
Phosphorodimorpholidic halides react with alcohols, yielding phosphoro dimorpholidates, which afford dihydrogen phosphates on mild acid hydrolysis. This method, which is particularly useful for the phosphorylation of unsaturated alcohols, has been used to synthesise ethyl, phenethyl, phenyl, *cyclo*hexyl, and the biologically important allyl and 2-(4-methyl-5-thiazolyl)-ethyl dihydrogen phosphate.

THE phosphorylating properties of phosphoramidic halides may be inferred from earlier chemical studies [1] and from more recent work on the toxicity of substances of this type.[2] Attempts to utilise phosphoramidic derivatives for preparative phosphorylation, however, have hitherto met little success.[3]




We have found that phosphoramidic halides derived from morpholine are valuable reagents for the phosphorylation of alcohols.[4] Phosphorodimorpholidic bromide and chloride (I; X = Br, Cl), prepared from morpholine and the respective phosphorus

[1] Michaelis, *Annalen*, 1903, **326**, 129; Michaelis and Schulze, *Ber.*, 1894, **27**, 2572.
[2] Saunders, "Some aspects of the chemistry and toxic action of organic compounds containing phosphorus and fluorine," Cambridge University Press, 1957, pp. 7, 87; cf. Riley, Turnbull, and Wilson, *J.*, 1957, 1373 and references cited therein.
[3] Zetzsche and Büttiker, *Ber.*, 1940, **73**, 47; Bevan, Brown, Gregory, and Malkin, *J.*, 1953, 127.
[4] Montgomery and Turnbull, *Proc. Chem. Soc.*, 1957, 178.

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oxyhalide, smoothly phosphorylated alcohols in the presence of an organic base, affording the phosphorodimorpholidates [II; R = Et, Ph·$CH_2$·$CH_2$, $CH_2$:CH·$CH_2$, $Me_2$C:CH·$CH_2$, 2-(4-methyl-5-thiazolyl)ethyl, *cyclo*hexyl, and cholesteryl]. The morpholidic bromide phosphorylated alcohols rapidly in the cold, the less reactive chloride only on prolonged heating.

A sterically hindered tertiary base was used throughout to avoid dealkylation.[5] 2 : 6-Lutidine was generally satisfactory although tribenzylamine was preferred for the preparation of *cyclo*hexyl phosphorodimorpholidate which tended to eliminate *cyclo*hexene in the presence of other bases. Ethyl, *cyclo*hexyl, and cholesteryl phosphorodimorpholidate were prepared independently from the respective phosphorodichloridate (III; R = Et, *cyclo*hexyl, and cholesteryl).

The morpholidates were converted into their dihydrogen phosphates [IV; R = Et, Ph·$CH_2$·$CH_2$, $CH_2$:CH·$CH_2$, 2-(4-methyl-5-thiazolyl)ethyl, and *cyclo*hexyl] by aqueous hydrolysis with a protonated ion-exchange resin, or, less smoothly, hydrochloric acid. Hydrolysis is thought to proceed by proton-attack on the morpholidate nitrogen atom, followed by P–N bond fission yielding successively the mono- and the di-hydrogen phosphates (VI and IV). The cations (V) and (VII) may be transiently involved. Consistently with this mechanism phenyl phosphorodimorpholidate (II; R = Ph), prepared from the phosphorodichloridate, afforded the intermediate phenyl hydrogen phosphoromorpholidate (VI; R = Ph) after brief contact with the resin, more prolonged treatment yielding phenyl dihydrogen phosphate (IV; R = Ph).

The phosphates were conveniently isolated as their *cyclo*hexylammonium or phenylacetamidinium salts. Allyl dihydrogen phosphate is of interest in relation to the metabolism of *Aspergillus niger*,[6] while 2-(4-methyl-5-thiazolyl)ethyl dihydrogen phosphate is an integral part of the cocarboxylase molecule.[7] Ethyl and *cyclo*hexyl dihydrogen phosphate were independently prepared from their phosphorodichloridates by hydrolysis.

Cholesteryl phosphorodimorpholidate (in aqueous propanol) was not hydrolysed by prolonged treatment with the resin. The lipophilic nature of the cholesteryl group appears to prevent interaction at the resin interface in the aqueous system employed. Treatment of the phosphorodimorpholidate with acetic, formic, or hydrochloric acids resulted in ($S_N1$) fission of the *O*–cholesteryl bond, yielding respectively cholesteryl acetate, formate, and chloride.[8]

Phosphoramidic halides derived from aromatic amines appear to be of limited value as phosphorylating agents. Phosphorodianilidic chloride (VIII; R = H, X = Cl) easily eliminates hydrogen chloride, yielding the phosphorophenylimidate.[9] *NN*-Dimethylphosphorodianilidic chloride (VIII; R = Me, X = Cl), prepared from methylaniline and phosphorus oxychloride, was stable in this respect, and reacted smoothly with ethanolic sodium ethoxide, yielding ethyl *NN'*-dimethylphosphorodianilidate (VIII; R = Me, X = OEt). The ester was recovered unchanged after prolonged treatment with the resin, suggesting that, in derivatives of this type, delocalisation of the lone-pair electrons on nitrogen by aromatic resonance protects the P–N bond from proton attack.

## Experimental

2 : 6-Lutidine was purified as described by Biddiscombe *et al.*[10] Phosphorus oxybromide was prepared by the method of Gerrard *et al.*[11] Phosphorylations were carried out in ethanol-free chloroform. Silica gel was washed successively with water, N-hydrochloric acid, water, and acetone, and activated at 110° for 15 hr.

[5] Atherton, Howard, and Todd, *J.*, 1948, 1106.
[6] Shin'ichirô Baba, *J. Agric. Chem. Soc. Japan*, 1943, **19**, 651; *Chem. Abs.*, 1951, **45**, 9114.
[7] Avison and Hawkins, *Quart. Rev.*, 1951, **5**, 179, and references cited therein.
[8] Montgomery, Turnbull, and Wilson, *J.*, 1956, 4603.
[9] Caven, *J.*, 1903, **83**, 1045; Zeile and Kruckenberg, *Ber.*, 1942, **75**, 1127.
[10] Biddiscombe, Coulson, Handley, and Herington, *J.*, 1954, 1957.
[11] Gerrard, Nechvatal, and Wyvill, *Chem. and Ind.*, 1947, 437.

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*Phosphorodimorpholidic Bromide.*—Morpholine (35 g.) was gradually added to phosphorus oxybromide (29 g.) in chloroform (120 c.c.) at 10°. The mixture was stirred at room temperature for 4 hr., filtered, and evaporated to *ca.* 50 c.c., and the resulting solution, which was moderately stable at 0° in the absence of moisture, used directly for phosphorylation

*Reaction of Phosphorodimorpholidic Bromide with Alcohols.*—(a) *Allyl alcohol.* The alcohol (3 c.c.), 2 : 6-lutidine (4 c.c.), and a solution (17·4 c.c.) of phosphorodimorpholidic bromide (from phosphorus oxybromide, 6·4 g.) were mixed at room temperature and set aside for 5 hr. Volatile components were removed in a vacuum, ether (40 c.c.) was added, and the solution filtered from base hydrobromide (2·9 g.), and distilled, affording *allyl phosphorodimorpholidate* (2·6 g.), b. p. 113—117°/0·002 mm., $n_D^{17}$ 1·4930 (Found: N, 9·85; P, 11·55. $C_{11}H_{21}O_4N_2P$ requires N, 10·1; P, 11·2%).

(b) *Ethyl alcohol.* The alcohol similarly yielded ethyl phosphorodimorpholidate, b. p. 102—108°/0·003 mm., hygroscopic prisms, m. p. 48° (from benzene–*cyclo*hexane) undepressed on admixture with a specimen prepared from ethyl phosphorodichloridate.

(c) *2-Phenylethanol.* The alcohol similarly yielded *phenethyl phosphorodimorpholidate*, a syrup, $n_D^{18\cdot5}$ 1·5231 (chromatographed on silica gel, and eluted with ethanol) (Found: N, 8·35. $C_{16}H_{25}O_4N_2P$ requires N, 8·2%).

(d) cyclo*Hexanol.* The alcohol, phosphorylated in the presence of tribenzylamine, yielded cyclo*hexyl phosphorodimorpholidate*, hygroscopic prisms (chromatographed on silica gel and crystallised from benzene–light petroleum), m. p. 53° (Found: C, 53·2; H, 8·8. $C_{14}H_{27}O_4N_2P$ requires C, 52·8; H, 8·6%) undepressed on admixture with a specimen prepared from *cyclo*hexyl phosphorodichloridate.

(e) *Prenol* (3 : 3-*dimethylallyl alcohol*). The alcohol similarly yielded 3 : 3-*dimethylallyl phosphorodimorpholidate*, a syrup (Found: N, 8·8. $C_{13}H_{25}O_4N_2P$ requires N, 9·2%).

(f) 2-(4-*Methyl-5-thiazolyl*)*ethyl alcohol.* The hydrochloride of the alcohol [12] (2·0 g.) was dissolved in chloroform (6 c.c.) and 2 : 6-lutidine (6 c.c.), and a chloroform solution (15 c.c.) of phosphorodimorpholidic bromide [from phosphorus oxybromide (4·5 g.)] added. The mixture was warmed at 40° for 15 min., water (0·3 c.c.) and excess of light petroleum were added, the whole was filtered from precipitated salts, and the filtrates were evaporated. The residue was dissolved in benzene and chromatographed on silica gel, affording 2-(*4-methyl-5-thiazolyl*)-*ethyl phosphorodimorpholidate* as a syrup (1·5 g.) (Found: N, 10·2. $C_{14}H_{24}O_4N_3PS$ requires N, 11·6). The *dipicrolonate*, crystallised from ethanol–ether, had m. p. 181° [Found: N, 17·3%; equiv. (by titration), 406. $C_{14}H_{24}O_4N_3PS,2C_{10}H_8O_5N_4$ requires N, 17·3%; equiv., 445].

*Phosphorodimorpholidic Chloride.*—Morpholine (71 g.) was added slowly to phosphorus oxychloride (19 c.c.) in benzene (200 c.c.) at 10—20°. The mixture was stirred for 3 hr., filtered, and evaporated, and the residue distilled in *ca.* 10 g. portions, affording the dimorpholidic chloride (32 g.), b. p. 137—140°/0·02 mm., m. p. 81° (from *cyclo*hexane) (Found: C, 37·1; H, 6·3; N, 10·6; Cl, 13·5. $C_8H_{16}O_3N_2PCl$ requires C, 37·7; H, 6·3; N, 11·0; Cl, 13·9%).

*Reaction of Phosphorodimorpholidic Chloride with Alcohols.*—(a) *With ethanol.* Ethanol (7 c.c.), 2 : 6-lutidine (4·5 c.c.), and phosphorodimorpholidic chloride (8·5 g.) were refluxed for 16 hr. The solution was evaporated, the residue extracted with ether, and the extract distilled, affording ethyl phosphorodimorpholidate, b. p. 112—123°/0·002 mm. (4 g.), m. p. 48° undepressed on admixture with a specimen prepared from ethyl phosphorodichloridate.

(b) *With cholesterol.* Cholesterol (5·4 g.), pyridine (10 c.c.), and phosphorodimorpholidic chloride (3·5 g.) were heated for 17 hr. in a carbon tetrachloride vapour bath (76°). The product was diluted with water, and the precipitate collected, affording *cholesteryl phosphorodimorpholidate* (3·7 g.), m. p. 153° (from light petroleum) (Found: C, 69·9; H, 10·1; N, 4·5; P, 5·4. $C_{35}H_{61}O_4N_2P$ requires C, 69·5; H, 10·2; N, 4·6; P, 5·1%).

*Phenyl Phosphorodimorpholidate.*—Prepared from phenyl phosphorodichloridate (1 mol.) by treatment with morpholine (4 mols.) in benzene at 20—30°, this was obtained as prisms, m. p. 84° (from *cyclo*hexane). Audrieth and Toy [13] give m. p. 85°.

*Cholesteryl Phosphorodimorpholidate.*—Cholesteryl phosphorodichloridate [9] (100 mg.) was warmed with morpholine (0·07 c.c.) in benzene (0·8 c.c.) for 1 hr. at 50—60°, then filtered. Evaporation yielded the morpholidate, m. p. 159° (from light petroleum), undepressed by admixture with a specimen prepared from phosphorodimorpholidic chloride.

*Ethyl Phosphorodichloridate.*—Ethanol (23 g.) was stirred into phosphorus oxychloride

[12] Williams, Waterman, Keresztesy, and Buchman, *J. Amer. Chem. Soc.*, 1935, **57**, 536.
[13] Audrieth and Toy, *ibid.*, 1942, **64**, 1337.

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(153 g.) at 0°, and the product distilled after 30 min., affording the dichloridate (41 g.), b. p. 62—65°/12 mm. Walczynska [14] gives b. p. 64—65°/10 mm.

*Reaction of Ethyl Phosphorodichloridate with Morpholine.*—Morpholine (27 g.) was gradually added to ethyl phosphorodichloridate (13 g.) in ether (200 c.c.) at 10—15°, and the product filtered, and evaporated to dryness affording *ethyl phosphorodimorpholidate* (7·2 g.), hygroscopic prisms, m. p. 48° (from benzene–*cyclo*hexane) (Found: N, 10·1. $C_{10}H_{21}O_4N_2P$ requires N, 10·6%).

cyclo*Hexyl Phosphorodichloridate.*—*cyclo*Hexanol (10 g.) and 2 : 6-lutidine (11 g.) in carbon tetrachloride (20 c.c.) were added to phosphorus oxychloride (15 g.) in carbon tetrachloride (100 c.c.) at 0—10°. After a further hour the product was filtered from base hydrochloride (17 g.) and evaporated, yielding the dichloridate as a colourless oil (20 g.) which decomposed on attempted distillation in a vacuum, with the production of *cyclo*hexene (b. p. 81°).

cyclo*Hexyl Phosphorodimorpholidate.*—The foregoing oil (10 g.) was mixed with carbon tetrachloride (160 c.c.), and morpholine (17 g.) added at 0—10°. The mixture was stirred for 2 hr. at room temperature, filtered, and evaporated, yielding the phosphorodimorpholidate (10 g.), hygroscopic prisms, m. p. 57° (from benzene–light petroleum) (Found: N, 8·9. Calc. for $C_{14}H_{27}O_4N_2P$: N, 8·8%).

*Hydrolysis of Phosphorodimorpholidates.*—Solutions of the foregoing phosphorodimorpholidates (500 mg.) in water (5 c.c.) were percolated slowly (1—2 hr.) through Amberlite IR-120 resin ($H^+$ form) at 60°. The following dihydrogen phosphates were obtained by evaporation:

(a) Ethyl dihydrogen phosphate, syrup (230 mg.). This gave a bis*cyclo*hexylammonium salt, m. p. 188° (from aqueous acetone), undepressed on admixture with a specimen prepared by hydrolysis of ethyl phosphorodichloridate (Found: N, 8.1. Calc. for $C_2H_7O_4P,2C_6H_{13}N$: N, 8·6%), and a *bis*(*phenylacetamidinium*) *salt*, plates (from ethereal ethanol), m. p. 157° (Found: N, 14·7. $C_2H_7O_4P,2C_8H_{10}N_2$ requires N, 14·2%).

(b) Phenyl dihydrogen phosphate (260 mg.) (from chloroform), m. p. 94°. This gave a bis(*cyclo*hexylammonium) salt, m. p. 211° undepressed on admixture with authentic specimens.

(c) *cyclo*Hexyl dihydrogen phosphate (240 mg.) (from benzene–*cyclo*hexane), m. p. 86°, identical with a specimen prepared by hydrolysis of *cyclo*hexyl phosphorodichloridate. Its *bis*cyclo*hexylammonium salt* had m. p. 212° (from ethanol) (Found: N, 7·5. $C_6H_{13}O_4P,2C_6H_{13}N$ requires N, 7·4%).

(d) *Allyl dihydrogen phosphate*, a syrup (250 mg.) [Equiv. (by titration), 75. $C_3H_7O_4P$ requires equiv., 69]. It gave a *bis*cyclo*hexylammonium salt*, m. p. 175° (decomp.) (from aqueous acetone) (Found: N, 7·9. $C_3H_7O_4P$, $2C_6H_{13}N$ requires N, 8·3%). We were unable to confirm the properties of allyl dihydrogen phosphate reported by Shin'ichirô Baba.[6]

(e) *Phenethyl dihydrogen phosphate*, a syrup (225 mg.) (Equiv., 103. $C_8H_{11}O_4P$ requires equiv., 101). It gave a *mono*cyclo*hexylammonium salt*, m. p. 177° (from aqueous acetone) (Found: N, 4·0%; equiv., 300. $C_8H_{11}O_4P,C_6H_{13}N$ requires N, 4·65%; equiv., 301).

(f) 2-(4-*Methyl*-5-*thiazolyl*)*ethyl dihydrogen phosphate* (105 mg.) (Equiv., 134. $C_6H_{10}O_4PNS$ requires equiv., 112). It gave an *acid* cyclo*hexylammonium salt*, m. p. 190° (from aqueous acetone) (Found: N, 7·2. $2C_6H_{10}O_4NSP,C_6H_{13}N,H_2O$ requires N, 7·45%).

*Phenyl Hydrogen Phosphoromorpholidate.*—Phenyl phosphorodimorpholidate (530 mg.) was treated in water (5 c.c.) with Amberlite IR-120 resin ($H^+$ form) during 30 min., and the solution evaporated, affording the hydrogen phosphoromorpholidate (290 mg.). The cyclo*hexylammonium salt*, m. p. 202° (from aqueous acetone), depressed the m. p. of bis(*cyclo*hexylammonium) phenyl phosphate (Found: N, 8·6. $C_{10}H_{14}O_4NP,C_6H_{13}N$ requires N, 8·2%).

cyclo*Hexyl Dihydrogen Phosphate.*—*cyclo*Hexyl phosphorodichloridate (10 g.) in carbon tetrachloride (50 c.c.) was treated with *tert.*-butyl alcohol (8·5 g.) and water (1·0 c.c.) for 30 min. at 50°. Removal of the solvent left an oil which was dissolved in a slight excess of saturated sodium hydrogen carbonate solution, filtered through Amberlite resin IR-120 ($H^+$ form), and evaporated to dryness, affording the *dihydrogen phosphate* (4·8 g.), m. p. 85° (from chloroform–*cyclo*hexane) (Found: C, 39·7; H, 7·5. $C_6H_{13}O_4P$ requires C, 40·0; H, 7·3%).

cyclo*Hexylammonium Di*cyclo*hexyl Phosphate.*—*cyclo*Hexanol (20 g.) and 2 : 6-lutidine (21 g.) in carbon tetrachloride (40 c.c.) were gradually added at 0° to phosphorus oxychloride (15 g.) and 2 : 6-lutidine (2 g.) in carbon tetrachloride (200 c.c.). The solution was set aside overnight, filtered, shaken with M-potassium hydrogen sulphate at 0°, and dried ($Na_2SO_4$),

[14] Walczynska, *Roczniki Chem.*, 1926, **6**, 110; *Chem. Abs.*, 1927, **21**, 2457.

and the solvent removed. The residue was heated with *tert.*-butyl alcohol (10·5 g.) at 90° for 30 min., evaporated at room temperature, extracted with 2·5N-sodium hydroxide (80 c.c.), acidified with acetic acid, and treated with *cyclo*hexylamine, affording the cyclo*hexylammonium salt*, needles (4·7 g.), m. p. 211° (from ethanol–ether) (Found: C, 59·9; H, 10·2; N, 3·9. $C_{12}H_{23}O_4P,C_6H_{13}N$ requires C, 59·8; H, 10·0; N, 3·9%).

*Solvolysis of Cholesteryl Phosphorodimorpholidate.*—(a) *With acetic acid.* The dimorpholidate (180 mg.) was refluxed with acetic acid for 50 hr. The product was diluted with water affording 3β-acetoxycholest-5-ene [3] (105 mg.; m. p. 112°).

(b) *With formic acid.* The dimorpholidate, heated with 90% formic acid at 100° for 20 min., similarly yielded 3β-formyloxycholest-5-ene, m. p. 94° (from ethanol), $[\alpha]_D$ −56°.

(c) *With hydrogen chloride.* The dimorpholidate, heated at 90° for 15 min. with 2N-hydrogen chloride in 80% aqueous acetic acid, similarly afforded 3β-chlorocholest-5-ene,[3] m. p. 88°.

NN′-*Dimethylphosphorodianilidic Chloride.*—Methylaniline (214 g.) was added to phosphorus oxychloride (77 g.) in toluene (220 c.c.), the mixture refluxed for 1 hr., cooled, filtered, and evaporated, and the residue distilled, affording the *phosphorodianilidic chloride* (90 g.), b. p. 149—151°/0·03 mm., $n_D^{20}$ 1·5851 (Found: N, 9·9. $C_{14}H_{16}ON_2PCl$ requires N, 9·5%).

*Ethyl* NN′-*Dimethylphosphorodianilidate.*—Ethanol (8 c.c.), the foregoing chloride (9·8 g.), and 2 : 6-lutidine (4·5 c.c.) were refluxed for 16 hr., then evaporated, the residue was extracted with ether, and the extracts were distilled, yielding the *phosphorodianilidate* (5·3 g.), b. p. 145—148°/0·03 mm., $n_D^{18}$ 1·5631 (Found: N, 9·2. $C_{16}H_{21}O_2N_2P$ requires N, 9·2%).

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CHEMISTRY DEPARTMENT, THE UNIVERSITY, BIRMINGHAM, 15. [*Received, December 5th*, 1957.]

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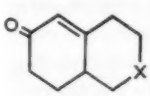
## 400. *Decahydroisoquinolines and Related Compounds. Part II.* Some Further Examples of Abnormal Ultraviolet Absorption.*

By C. B. CLARKE and A. R. PINDER.

Ultraviolet-absorption studies on a series of basic αβ-unsaturated ketones have shown that the compounds absorb at abnormally short wavelengths. The effect is enhanced by quaternisation of the basic groups. Possible explanations of the behaviour are discussed.

ATTENTION has been drawn [1,2] to the fact that the basic αβ-unsaturated ketone 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-2-methyl-6-oxo*iso*quinoline (I; X = NMe) absorbs maximally in the ultraviolet region at an abnormally short wavelength. Similar behaviour has been reported [2] for a 1-aryl derivative of compound (I; X = NH) and very recently [3] for the thio*iso*chroman (I; X = S).

It seemed from these observations that this behaviour might be general for αβ-unsaturated ketones containing basic and possibly other electron-donating groups, not directly united with the chromophore, but separated from it by a saturated carbon chain. We have now prepared a series of basic αβ-unsaturated ketones, and find that such compounds do absorb maximally at unexpectedly short wavelengths, the magnitude of the hypsochromic effect depending on the length of the intervening carbon chain. The effect is also observed with an *N*-acetylated ketonic base, and is enhanced by quaternisation of the nitrogen atom or conversion into the amine oxide. The compounds studied, which may be formulated by the general expression $>N\cdot[C]_n\cdot C{=}C{-}C{=}O$, and the absorptions, are summarised in the Table. Comparison has been made in each case with the value of $\lambda_{max.}$



(I)

* Part I, *J.*, 1956, 327.

[1] Marchant and Pinder, *Chem. and Ind.*, 1953, 1366; 1954, 1261; *J.*, 1956, 327.
[2] Georgian, *Chem. and Ind.*, 1954, 930.
[3] *Idem, ibid.*, 1957, 1480.

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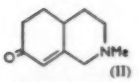
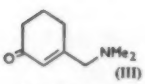
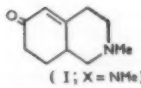
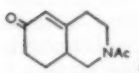
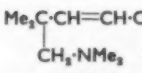
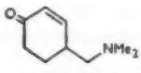
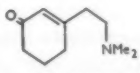
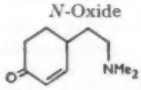
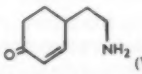
calculated by use of Woodward's rules for the prediction of the position of maximum absorption,[4] or with the observed value for a model αβ-unsaturated ketone (cf. Table).

The cyclic ketones were prepared by reduction, with sodium and liquid ammonia, of a series of aminoalkyl derivatives of anisole, followed by acid hydrolysis.[5] The reduction of 1 : 2 : 3 : 4-tetrahydro-7-methoxy-2-methyl*iso*quinoline afforded the hexahydro-derivative (XII), which was crystalline and on hydrolysis yielded mainly the reduced *iso*quinolone (II), though infrared measurements indicated the presence of a small quantity of the unconjugated ketone (XIII) even after prolonged acid hydrolysis. Catalytic hydrogenation of the ketone (II) gave the corresponding decahydro-oxo*iso*quinoline (XIV), which showed normal infrared carbonyl absorption, indicating that there is no transannular amide-type interaction between the carbonyl group and the nitrogen atom.[6] Similar normal behaviour is shown by the reduction products of several of the ketones studied.

3-Dimethylamino-2 : 2-dimethylpropionaldehyde (XV) was obtained from *iso*butyraldehyde by a Mannich reaction. Condensation with acetone then afforded 6-dimethylamino-5 : 5-dimethylhex-3-en-2-one (IX).

*Ultraviolet absorption* (mμ) *of basic αβ-unsaturated ketones and related compounds in methanol.*

| Ketone | $\lambda_{max.}$ obs.† | $\lambda_{max.}$ calc. | $-\Delta\lambda$ |
|---|---|---|---|
|  (II) | 222 | 244 | 22 |
| Methiodide | 218 | 244 | 26 |
|  (III) | 225 | 239 | 14 |
| Methiodide | 222 | 239 | 17 |
|  (I; X = NMe) | 227·5 | 244 | 16·5 |
| Methiodide [1–3] | 222 | 244 | 22 |
|  (IV) | 234 | 244 | 10 |
|  (IX) | 222 | 227 | 5 |
| Methiodide | 220 | 227 | 7 |

| Ketone | $\lambda_{max.}$ obs.† | $\lambda_{max.}$ calc. | $-\Delta\lambda$ |
|---|---|---|---|
|  (V) | 225 | 227 | 2 |
| Methiodide | 220 | 227 | 7 |
|  (VI) | 228·5 | 239 | 10·5 |
| Methiodide | 221 | 239 | 18 |
| *N*-Oxide | 220 | 239 | 19 |
|  (VII) | 224 | 227 | 3 |
| Methiodide | 220 | 227 | 7 |
|  (VIII) | 224 | 227 | 3 |
| $Et_2N{\cdot}CH_2{\cdot}CH{=}CH{\cdot}COMe$ (X) | 218 | 224 * | 6 |
| $Et_2N{\cdot}CH_2{\cdot}CH{=}CH{\cdot}COPh$ (XI) | 248 | 256 ** | 8 |

* Observed value for ethylideneacetone (Evans and Gillam, *J.*, 1941, 815).
** Observed value for crotonophenone (Mariella and Raube, *J. Amer. Chem. Soc.*, 1952, **74**, 521).
† log $\varepsilon_{max.}$ 3·7—4·1 (bases), 4·2—4·4 (methiodides).

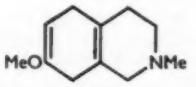
5-Diethylaminopent-3-en-2-ol (XVI; R = Me) was synthesised from but-3-yn-2-ol, which was converted into its acetate and thence *via* a Mannich reaction into 4-acetoxy-1-diethylaminopent-2-yne (XVII). Hydrolysis followed by partial hydrogenation with Lindlar's catalyst afforded the alcohol (XVI; R = Me), which presumably has the *cis*-configuration.[7] Attempts to oxidize this compound to the ketone (X) with chromic acid

[4] Woodward, *J. Amer. Chem. Soc.*, 1941, **63**, 1123; 1942, **64**, 76.
[5] Cf. Birch, *J.*, 1944, 430, and later papers.
[6] Cf. Anet, Bailey, and Robinson, *Chem. and Ind.*, 1953, 944; Leonard and co-workers, *J. Amer. Chem. Soc.*, 1954, **76**, 630, 3463, 5708.
[7] Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworths, London, 1955, pp. 26, 201.

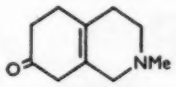
or manganese dioxide gave an impure product containing some (X), as shown by the ultraviolet absorption, but the product showed a strong infrared band in the OH and NH region. This may be explained by incomplete oxidation or, more probably, in view of recent observations of the oxidation of tertiary amines by manganese dioxide,[8] by oxidative attack of the $NEt_2$ group with formation of the formyl derivative of the corresponding primary amine: $R{\cdot}NEt_2 \xrightarrow{O} R{\cdot}NH{\cdot}CHO + Me{\cdot}CHO$. An analogous series of reactions with 1-phenylprop-1-yn-1-ol resulted in 4-diethylamino-1-phenylbut-2-en-1-ol (XVI; R = Ph); this alcohol behaved similarly on oxidation, yielding a mixture of products containing some of the corresponding ketone (XI).

2-Acetyl-1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-6-oxo*iso*quinoline (IV) was obtained from 1 : 2 : 3 : 4-tetrahydro-6-methoxy*iso*quinoline by reduction with sodium and liquid ammonia, followed by acetylation and partial hydrolysis.

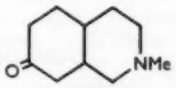
It is apparent from the Table that when the nitrogen atom is separated from the chromophore by a single carbon atom a strong hypsochromic effect is in most cases observed (6—22 mμ). Quaternisation of the nitrogen atom enhances the effect by a further 4—5 mμ. When two carbon atoms separate the groups the shift is smaller (2—10·5 mμ), and is again enhanced by quaternisation or conversion into the amine oxide, but



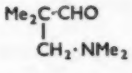
(XII)



(XIII)



(XIV)



(XV)

is reduced by neutralisation of the basic character of the nitrogen atom by acetylation. It is rather surprising that 4-dimethylaminomethyl*cyclo*hex-2-en-1-one (V) shows a very small effect, but this is in harmony with the observation that thebainone-A (XVIII) shows a similarly small shift.[3] When there are more than two carbon atoms between nitrogen atom and chromophore the hypsochromic shift is very small, but even in these cases quaternisation causes a measurable effect.

An explanation of the hypsochromic effect shown by the quaternary salts and the amine oxide [and also by the sulphonium salt (I; X = $^+$SMe) and the sulphone [3] (I; X = $SO_2$)] does not seem to present any difficulty. Presumably the strong electron-attracting inductive influence of the positive centre is transmitted through the carbon chain to the chromophore, as, for example, in the nitration [9] of quaternary ammonium salts of the type Ph·$[CH_2]_n{\cdot}NMe_3^+$ (several other cases of interaction between groups through a saturated carbon chain are known [10]).

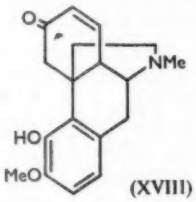
The behaviour of the ketonic bases is not so readily accounted for. Amino-groups of the type $>NR$ and $-NR_2$ (R = H or alkyl) are known to be electron-attracting in an inductive sense,[11] and perhaps the hypsochromic effects could here also be explained in terms of an inductive effect. However, the basic group is not strongly electrophilic, especially compared with a positively charged group, and there is only a small extra hypsochromic effect associated with the establishment of a positive charge on the nitrogen atom. Further, the *N*-acetyl ketone (IV) shows a smaller hypsochromic shift than the base (I; X = NMe), whereas owing to resonance of the type $>\overset{+}{N}{-}C(=O^-){-}CH_3$ in the amide it was to be expected that this compound would absorb maximally at no longer a wavelength than does the base (I; X = NMe), if an inductive effect solely is at play.

[8] Henbest and Thomas, *Chem. and Ind.*, 1956, 1097.
[9] Goss, Ingold, and Wilson, *J.*, 1926, 2440; Goss, Hanhart, and Ingold, *J.*, 1927, 250; Ingold and Wilson, *ibid.*, p. 810.
[10] Braude, *J.*, 1949, 1902; Jeffrey, *Proc. Roy. Soc.*, 1947, *A*, **188**, 222; Bateman and Jeffrey, *Nature*, 1943, **152**, 446; Nielsen, *Chem. and Ind.*, 1957, 1358.
[11] Waters, "Physical Aspects of Organic Chemistry," Routledge, 2nd Edition, 1937, p. 209.

In Part I it was postulated that for the free bases the hypsochromic effect was due to the contribution to the stable state of the molecules made by dipolar structures such as (XIX). The reduction in the effect accompanying *N*-acylation may then be attributed to a decrease in the electron-donating capacity of the nitrogen atom as a result of the resonance described. However, the existence of the ketone (XX) in a dipolar form (XXI) has been offered as an explanation of a bathochromic shift, *viz.*, the maximal

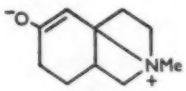
$Et_2N{\cdot}CH_2CH{=}CH{\cdot}CHR{\cdot}OH$ (XVI)

$Et_2N{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}CHMe{\cdot}OAc$ (XVII)

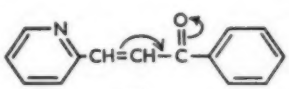


(XVIII)

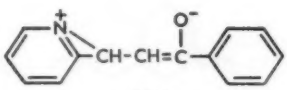
absorption of the ketone at a longer wavelength than that for the corresponding 3- and 4-isomer (all three ketones, however, showing strong hypsochromic shifts relative to benzylideneacetophenone).[12]



(XIX)



(XX)



(XXI)

The ultraviolet absorption of dipolar structures such as (XIX) may be regarded as that of a single ethylenic bond bearing a highly polar oxygen substituent. A model for comparison would be the enolate anion of a monoketone, but the spectra of such structures seem not to have been recorded. There can be little doubt, however, that the substituent will have a strong bathochromic effect, so that maximal absorption will be shifted from the 175 mμ region, characteristic of ethylene, to the 220—240 mμ region (cf. $CHMe{=}CH{\cdot}CO_2H$ and $MeO{\cdot}CMe{=}CH{\cdot}CO_2H$, $\Delta\lambda_{max.}$ +30 mμ; $CH_2{=}CH_2$ and $CH_2{=}CH{\cdot}S{\cdot}CH_2{\cdot}CH_2Cl$, $\Delta\lambda_{max.}$ +53 mμ).[13]

The observed infrared absorption of the bases is normal for αβ-unsaturated ketones. This is difficult to explain on the basis of the dipolar structures. Recent studies on the infrared absorption of enolate anions show that enolisable compounds such as acetylacetone show no carbonyl stretching band in the 1715 $cm.^{-1}$ region, and have strong enolate anion bands in the 1660 $cm.^{-1}$ region.[14] The basic ketones here investigated all show carbonyl bands in the 1665—1685 $cm.^{-1}$ region, and no enolate anion bands.

## Experimental

Unless otherwise stated, ultraviolet absorption data refer to solutions in methanol, and infrared data to liquid film or Nujol mulls, and methiodides crystallised from ethanol in needles.

1 : 2 : 3 : 4-*Tetrahydro*-7-*methoxy*-2-*methylisoquinoline*.—Platinum oxide catalyst (0·35 g.), suspended in glacial acetic acid (25 c.c.), was pre-reduced by hydrogen at room temperature and pressure. 7-Methoxy*iso*quinoline [15] (4·0 g.) in acetic acid (50 c.c.) was added and reduction effected for 12 hr. (absorption 2 mols.). The filtered solution was concentrated under reduced pressure from the water-bath, the residual syrup dissolved in a little water, and the solution basified. 1 : 2 : 3 : 4-Tetrahydro-7-methoxy*iso*quinoline, isolated with ether, distilled at 146°/11 mm. (3·5 g.) (hydrochloride, m. p. 228—229°) (lit.: [15] b. p. 184—186°/50 mm.; hydrochloride, m. p. 228—229°). Methylation [16] of the base (6·8 g.) with 90% formic acid (5·8 g.)

[12] Coleman, *J. Org. Chem.*, 1956, **21**, 1193; Marvel and Stille, *ibid.*, 1957, **22**, 1451.
[13] Braude, *Ann. Reports*, 1945, **42**, 119; Bowden, Braude, and Jones, *J.*, 1946, 948.
[14] Bender and Figueras, *J. Amer. Chem. Soc.*, 1953, **75**, 6304.
[15] Fritsch, *Annalen*, 1895, **286**, 1.
[16] Cf. Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571.

XUM

and 35% aqueous formaldehyde (2·5 g.) for 8 hr. at 95—100° gave, after basification and ether-extraction, 1 : 2 : 3 : 4-tetrahydro-7-methoxy-2-methyl*iso*quinoline (5·6 g.), b. p. 131—135°/10 mm. (hydrochloride, m. p. 205°) (lit.: [15] b. p. 179°/50 mm.; hydrochloride, m. p. 201—202°).

1 : 2 : 3 : 4 : 5 : 8-*Hexahydro-7-methoxy-2-methyl*isoquinoline (XII).—The following conditions are typical of the sodium–liquid ammonia reductions described in this paper. The foregoing tertiary base (3·75 g.) in methanol (15 c.c.) was added gradually, with stirring, to liquid ammonia (300 c.c.) containing dry ether (20 c.c.), followed by sodium (3·0 g.) in small pieces during 1 hr. When all the sodium had dissolved, ether (100 c.c.) was added, followed by water (100 c.c.), and after being kept overnight the solution was thoroughly extracted with ether, and the combined extracts were dried and evaporated. The residual 1 : 2 : 3 : 4 : 5 : 8-*hexahydro-7-methoxy-2-methyl*isoquinoline distilled at 126°/8 mm., 140°/10 mm. (3·4 g.), solidified, and separated from light petroleum (b. p. 40—60°) in needles, m. p. 50—51° (Found: C, 73·7; H, 9·3. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·5%). The *methiodide*, formed readily by mixing the base with methyl iodide, had m. p. 222° (Found: C, 44·8; H, 6·3. $C_{12}H_{20}ONI$ requires C, 44·9; H, 6·2%).

1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro-2-methyl-7-oxo*isoquinoline (II).—The above hexahydro-base (2·0 g.) was boiled under reflux for 5 hr. with 2N-sulphuric acid (75 c.c.). The cooled solution was basified and the product isolated with ether. 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro-2-methyl-7-oxo*isoquinoline distilled at 58—60°/0·05 mm. (1·3 g.) (Found: C, 72·4; H, 9·0. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1%), $\lambda_{max.}$ 222 mμ (ε 5100), infrared carbonyl bands at 1665 (strong) and 1710 cm.$^{-1}$ (weak). The *methiodide* formed pale cream prisms, m. p. 205—208° (Found: C, 43·0; H, 5·7. $C_{11}H_{18}ONI$ requires C, 43·0; H, 5·9%), $\lambda_{max.}$ 218 mμ (ε 22,400).

*Decahydro-2-methyl-7-oxo*isoquinoline (XIV).—The preceding keto-base (1·0 g.) in acetic acid (20 c.c.) was shaken with Adams platinum oxide in hydrogen at room temperature and pressure for 3 hr. (uptake 1 mol.). The solution was filtered and evaporated and the residue taken up in a little water. *Decahydro-2-methyl-7-oxo*isoquinoline, isolated by basification and ether-extraction, distilled at 61—63°/0·03 mm. (0·85 g.) (Found: C, 71·8; H, 9·9. $C_{10}H_{17}ON$ requires C, 71·9; H, 10·2%). Infrared absorption: strong carbonyl band at 1703 cm.$^{-1}$. The *methiodide* had m. p. 258—259° (Found: C, 42·7; H, 6·8. $C_{11}H_{20}ONI$ requires C, 42·7; H, 6·5%).

3-*Dimethylaminomethyl*cyclo*hex-2-enone* (III).—3-Methoxybenzylamine (10·0 g.), obtained by the reduction of *m*-anisaldoxime,[17] was methylated with 90% formic acid (16·8 g.) and 40% formaldehyde (6·5 g.) during 7 hr. at 95—100°. Basification of the cooled solution, followed by ether-extraction, afforded 3-methoxy-*NN*-dimethylbenzylamine, b. p. 106°/10 mm. (4·6 g.) (lit.,[18] b. p. 105°/13 mm.) [*methiodide*, m. p. 142—143° (Found: C, 42·6; H, 6·0. $C_{11}H_{18}ONI$ requires C, 43·0; H, 5·9%)]. Reduction of the tertiary base (4·0 g.) with sodium (3·9 g.) in liquid ammonia (300 c.c.) containing methanol (20 c.c.) gave 3-*dimethylaminomethyl*-2 : 5-*dihydroanisole*, b. p. 93—96°/8 mm. (3·2 g.) (Found: C, 71·7; H, 10·1. $C_{10}H_{17}ON$ requires C, 71·9; H, 10·2%) [*methiodide*, m. p. 145° (Found: C, 42·7; H, 6·2. $C_{11}H_{20}ONI$ requires C, 42·7; H, 6·5%)]. Hydrolysis of the dihydro-base (2·0 g.) by boiling 2N-sulphuric acid (75 c.c.) for 1 hr. gave 3-*dimethylaminomethyl*cyclo*hex-2-enone*, b. p. 116—118°/22 mm. (1·2 g.) (Found: C, 70·8; H, 9·7. $C_9H_{15}ON$ requires C, 70·6; H, 9·8%), $\lambda_{max.}$ 225 mμ (ε 5950) [*methiodide*, m. p. 170—171° (Found: C, 40·8; H, 6·3. $C_{10}H_{18}ONI$ requires C, 40·7; H, 6·1%), $\lambda_{max.}$ 222 mμ (ε 23,600)].

4-*Dimethylaminomethyl*cyclo*hex-2-enone* (V).—Methylation of 4-methoxybenzylamine [19] (9·0 g.) with 90% formic acid (10·0 g.) and 40% formaldehyde (13·0 g.) for 3 hr. gave *NN*-dimethylanisylamine, b. p. 106—108°/11 mm. (8·5 g.) (lit.,[18] b. p. 109°/13 mm.). Reduction of the tertiary base (8·5 g.) with sodium (7·4 g.) in liquid ammonia (300 c.c.) and methanol (25 c.c.) afforded 4-*dimethylaminomethyl*-2 : 5-*dihydroanisole*, b. p. 100—102°/11 mm. (7·2 g.) (Found: C, 71·5; H, 9·9. $C_{10}H_{17}ON$ requires C, 71·9; H, 10·2%) [*methiodide*, in plates, m. p. 233—234° (decomp.) (Found: C, 42·8; H, 6·6. $C_{11}H_{20}ONI$ requires C, 42·7; H, 6·5%)]. Hydrolysis of the dihydro-base (2·0 g.) with 2N-hydrochloric acid (75 c.c.) refluxing under nitrogen for 1 hr. gave two products separated by fractional distillation. The first fraction, b. p. 60—64°/9 mm. (0·5 g.), was nitrogen-free and neutral, gave a positive reaction towards Brady's reagent, and quickly polymerised to a gelatinous material; it was probably 4-methylene*cyclo*hex-2-enone.

[17] Shoppee, *J.*, 1932, 696.
[18] Stedman, *J.*, 1927, 1904.
[19] Jones and Pyman, *J.*, 1925, **127**, 2592, 2596.

XUM

The main fraction, b. p. 104—105°/9 mm. (1·4 g.) (Found: C, 71·1; H, 10·2. $C_9H_{15}ON$ requires C, 70·6; H, 9·8%), was 4-*dimethylaminomethyl*cyclo*hex*-2-*enone*, $\lambda_{max.}$ 225 mμ (ε 6140). The 2 : 4-*dinitrophenylhydrazone*, prepared in alcoholic sulphuric acid with subsequent basification with potassium hydrogen carbonate, separated from ethanol in deep red needles, m. p. 131—133° (Found: C, 54·7; H, 5·7. $C_{15}H_{19}O_4N_5$ requires C, 54·1; H, 5·7%) [*methiodide*, m. p. 171—171·5° (Found: C, 40·8; H, 5·7. $C_{10}H_{18}ONI$ requires C, 40·7; H, 6·1%), $\lambda_{max.}$ at 220 mμ (ε 25,000)].

3-2′-*Dimethylaminoethyl*cyclo*hex*-2-*enone* (VI).—3-Methoxy-*NN*-dimethylphenethylamine [20] (4·0 g.), when reduced with sodium (3·1 g.) in liquid ammonia (300 c.c.) containing dry ether (25 c.c.) and methanol (25 c.c.), gave 3-2′-*dimethylaminoethyl*-2 : 5-*dihydroanisole*, b. p. 126°/14 mm. (3·2 g.) (Found: C, 72·8; H, 10·3. $C_{11}H_{19}ON$ requires C, 72·9; H, 10·5%) [*methiodide*, m. p. 139·5—140·5° (Found: C, 44·3; H, 6·7. $C_{12}H_{22}ONI$ requires C, 44·6; H, 6·8%]. Hydrolysis of the reduced base (1·0 g.) by boiling 2N-sulphuric acid (40 c.c.) for 1 hr. afforded 3-2′-*dimethylaminoethyl*cyclo*hex*-2-*enone*, b. p. 140°/19 mm. (0·75 g.) (Found: C, 72·4; H, 10·0. $C_{10}H_{17}ON$ requires C, 71·9; H, 10·2%), $\lambda_{max.}$ 228·5 mμ (ε 8500) [*methiodide*, plates, m. p. 176—177° (Found: C, 42·9; H, 6·2. $C_{11}H_{20}ONI$ requires C, 42·7; H, 6·5%), $\lambda_{max.}$ 221 mμ (ε 16,000)]. The N-*oxide* was obtained by mixing the base (0·74 g.) in ethanol (10 c.c.) with 30% hydrogen peroxide (0·7 c.c.). After 2 days at room temperature the solution was treated with charcoal, filtered, and evaporated, leaving the oxide as a neutral thick syrup (0·7 g.), $\lambda_{max.}$ 220 mμ (ε 8000). Passage of sulphur dioxide for several hours through an aqueous solution of the product regenerated, on basification, the original base (methiodide, m. p. and mixed m. p. 176—177°). Hydrogenation of the unsaturated ketonic base (0·5 g.) in ethanol (15 c.c.) with 5% palladised charcoal (200 mg.) for 2 hr. at room temperature and pressure (uptake 1 mol.) afforded 3-2′-*dimethylaminoethyl*cyclo*hexanone*, b. p. 134—136°/19 mm. (0·5 g.) (Found: C, 70·8; H, 11·4. $C_{10}H_{19}ON$ requires C, 71·0; H, 11·2%). Infrared absorption: strong carbonyl bands at 1700 cm.$^{-1}$ (liquid film) and 1718 cm.$^{-1}$ (in $CCl_4$).

The *methiodide* had m. p. 185° (decomp.) (Found: C, 42·2; H, 7·0. $C_{11}H_{22}ONI$ requires C, 42·4; H, 7·1%) and a strong infrared carbonyl band at 1705 cm.$^{-1}$ (in Nujol).

4-2′-*Dimethylaminoethyl*cyclo*hex*-2-*enone* (VII).—Reduction of *p*-methoxy-ω-nitrostyrene [21] (4·0 g.) in dry ether (100 c.c.) with lithium aluminium hydride (3·0 g.) suspended in dry ether (150 c.c.), under the usual conditions,[22] gave 4-methoxyphenethylamine, b. p. 126—128°/10 mm. (2·6 g.) (lit.,[23] b. p. 136°/16 mm.). Methylation [20] of the base with 98% formic acid (14·7 g.) and 40% formaldehyde (12·1 g.) afforded *O*-methylhordenine, b. p. 84°/0·5 mm., 108°/11 mm. (8·2 g.) (lit.,[24] b. p. 253—254°). Reduction of *O*-methylhordenine (8·15 g.) in methanol (30 c.c.) with sodium (6·5 g.) in liquid ammonia (350 c.c.) furnished 2 : 5-*dihydro*-O-*methylhordenine*, b. p. 124°/11 mm. (6·2 g.) (Found: C, 72·7; H, 10·5. $C_{11}H_{19}ON$ requires C, 72·9; H, 10·5%). Hydrolysis of the dihydro-base (1·7 g.) with boiling 2N-sulphuric acid (75 c.c.) for 1 hr. gave, after basification, 4-2′-*dimethylaminoethyl*cyclo*hex*-2-*enone*, b. p. 122°/11 mm. (1·2 g.) (Found: C, 71·6; H, 10·5. $C_{10}H_{17}ON$ requires C, 71·9; H, 10·2%), $\lambda_{max.}$ 224 mμ (ε 4150). Infrared absorption: strong carbonyl band at 1670 cm.$^{-1}$, weak band (unconjugated carbonyl group ?) at 1710 cm.$^{-1}$. The *methiodide* had m. p. 191° (Found: C, 42·1; H, 6·6. $C_{11}H_{20}ONI$ requires C, 42·7; H, 6·5%), $\lambda_{max.}$ 220 mμ (ε 15,500).

A similar reduction of 4-methoxyphenethylamine (5·0 g.) in methanol (25 c.c.) with sodium (4·0 g.) in liquid ammonia (300 c.c.) gave 2 : 5-*dihydro*-4-*methoxyphenethylamine*, b. p. 140°/16 mm. (3·6 g.) (Found: N, 9·1. $C_9H_{15}ON$ requires N, 9·15%), which with boiling 2N-sulphuric acid (100 c.c.) under nitrogen afforded, in 1 hr., 4-2′-*aminoethyl*cyclo*hex*-2-*enone* (VIII), b. p. 124°/11 mm. (2·7 g.) (Found: C, 69·0; H, 9·5. $C_8H_{13}ON$ requires C, 69·1; H, 9·4%), $\lambda_{max.}$ at 224 mμ (ε 6000). The *picrolonate* separated from methanol in yellowish-brown needles, m. p. 185—186° (Found: C, 53·7; H, 5·2. $C_{18}H_{21}O_6N_5$ requires C, 53·6; H, 5·2%).

3-*Dimethylamino*-2 : 2-*dimethylpropionaldehyde* (XV).[25]—*iso*Butyraldehyde (50 g.) and 25% aqueous dimethylamine (100 g.) were mixed and stirred at 25—30° during addition of 40%

[20] Haworth, Lamberton, and Woodcock, *J.*, 1947, 182; Davies, Haworth, Jones, and Lamberton, *ibid.*, p. 191.
[21] Rosemund, *Ber.*, 1909, **42**, 4780; see also Gairaud and Lappin, *J. Org. Chem.*, 1953, **18**, 1.
[22] Compare Hamlin and Weston, *J. Amer. Chem. Soc.*, 1949, **71**, 2210; Erne and Ramirez, *Helv. Chim. Acta*, 1950, **33**, 912.
[23] Schales, *Ber.*, 1935, **68***B*, 1943.
[24] Kindler and Hesse, *Arch. Pharm.*, 1927, **265**, 389.
[25] Cf. Mannich, Lesser, and Silten, *Ber.*, 1932, **65**, 378; see also "Organic Reactions," Vol. I, p. 330.

aqueous formaldehyde (150 g.) over 1 hr. After a further hour at room temperature, then 2 hr. on the water-bath, the mixture was cooled, treated with sodium chloride (150 g.) and potassium carbonate (100 g.), and extracted with ether. The dried extract was concentrated and the residue distilled *in vacuo* through a short Vigreux column. The main fraction was 3-dimethylamino-2 : 2-dimethylpropionaldehyde, b. p. 110—116°/100 mm. (39·7 g.) (lit.,[25] b. p. 142—144°/760 mm.).

6-*Dimethylamino*-5 : 5-*dimethylhex*-3-*en*-2-*one* (IX).—To a solution from sodium (2·5 g.) in absolute ethanol (40 c.c.) cooled to 0° was added the above Mannich base (12·9 g.) mixed with dry acetone (5·8 g.).[26] After the whole had been kept overnight at room temperature water was added, followed by potassium carbonate. 6-*Dimethylamino*-5 : 5-*dimethylhex*-3-*en*-2-*one*, isolated with ether, distilled at 102—104°/10 mm. (4·0 g.) (Found: C, 70·4; H, 11·0. $C_{10}H_{19}ON$ requires C, 71·0; H, 11·2%), and had $\lambda_{max.}$ 222 mμ (ε 13,400) [*methiodide*, m. p. 166—167° (Found: C, 42·7; H, 6·7. $C_{11}H_{22}ONI$ requires C, 42·4; H, 7·1%), $\lambda_{max.}$ 220 mμ (ε 25,950)].

2-*Acetyl*-1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydro*-6-*oxoisoquinoline* (IV).—Reduction of 1 : 2 : 3 : 4-tetrahydro-6-methoxy*iso*quinoline (3·2 g.) [27] with sodium (3·8 g.) in liquid ammonia (400 c.c.) containing ether (40 c.c.) and methanol (40 c.c.) gave the corresponding hexahydro-base, b. p. 138—140°/14 mm. (3·0 g.). Acetic anhydride (7 c.c.) was added slowly with ice-cooling to this base (2·4 g.), and the mixture kept at room temperature for 10 min. Acetic acid and excess of anhydride were removed *in vacuo* on the water-bath, and the residual 2-*acetyl*-1 : 2 : 3 : 4 : 5 : 8-*hexahydro*-6-*methoxy*isoquinoline distilled (b. p. 132°/0·1 mm.; 2·9 g.). This solidified and separated from methanol in needles, m. p. 70—71° (Found: C, 69·0; H, 8·0. $C_{12}H_{17}O_2N$ requires C, 69·6; H, 8·2%). Hydrolysis of the product by refluxing N-sulphuric acid (40 c.c.) for 30 min., gave, after saturation with ammonium sulphate and ether-extraction, 2-*acetyl*-1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydro*-6-*oxoisoquinoline*, b. p. 146—148°/0·7 mm. (0·6 g.) (Found: C, 68·3; H, 8·5; *N*-acetyl, 21·4. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8; *N*-acetyl, 22·4%), $\lambda_{max.}$ 234 mμ (ε 7860).

5-*Diethylaminopent*-3-*yn*-2-*ol*.—But-3-yn-2-ol (20·0 g.) and acetic anhydride (40 c.c.) were heated at 105—115° for 3 hr. The excess of anhydride was removed *in vacuo* and the residual 1-methylprop-2-ynyl acetate distilled [b. p. 125—127° (24·5 g.)] (lit.,[28] b. p. 124—126°). The acetate (10·0 g.), dry dioxan (45 c.c.), paraformaldehyde (4·1 g.), and anhydrous diethylamine (8·2 g.) were heated on the water-bath for 24 hr. The solvent was removed *in vacuo*, ether (100 c.c.) added, and the mixture extracted exhaustively with dilute hydrochloric acid. Basification and ether-extraction of the acid solution afforded 4-*acetoxy*-1-*diethylaminopent*-2-*yne* (XVII), b. p. 126°/23 mm. (16·0 g.) (Found: C, 66·9; H, 9·4. $C_{11}H_{19}O_2N$ requires C, 67·0; H, 9·6%). The ester (15·0 g.) in methanol (60 c.c.) was treated with 0·1M-methanolic sodium methoxide (15 c.c.), and the solution kept at room temperature for 12 hr. Evaporation *in vacuo* followed by treatment with water and ether extraction gave 5-*diethylaminopent*-3-*yn*-2-*ol*, b. p. 112—114°/10 mm. (10·5 g.) (Found: C, 69·1; H, 11·0. $C_9H_{17}ON$ requires C, 69·7; H, 11·0%).

5-*Diethylaminopent*-3-*en*-2-*ol* (XVI; R = Me).—The above aminopentenol (5·0 g.) in ethyl acetate (100 c.c.) was shaken in hydrogen at room temperature and pressure with Lindlar's catalyst [29] (0·75 g.). After 30 min. (absorption 1 mol.) the solution was filtered and evaporated under reduced pressure. The residual 5-*diethylaminopent*-3-*en*-2-*ol* distilled at 109—110°/10 mm. (4·4 g.) (Found: C, 68·6; H, 12·3. $C_9H_{19}ON$ requires C, 68·8; H, 12·1%). The *picrolonate*, obtained from benzene solutions, separated from methanol in brownish-yellow prisms, m. p. 138—139° (Found: C, 53·9; H, 6·1. $C_{19}H_{27}O_6N_5$ requires C, 54·2; H, 6·4%).

Oxidation of the above alcohol (2·0 g.) in acetic acid (4 c.c.) with chromium trioxide (0·9 g.) in acetic acid (4 c.c.) and water (2 c.c.) at 55° for 2½ hr., then at room temperature for 12 hr., gave, on basification and ether-extraction, a pale yellow oil, b. p. 104°/18 mm. (0·8 g.) (Found: C, 67·1; H, 12·0. Calc. for $C_9H_{17}ON$: C, 69·7; H, 11·0%). This could not be purified satisfactorily; it showed the properties of an αβ-unsaturated ketone (max. at 218 mμ; ε 2900), but the infrared absorption (liquid film) showed a strong band at 3130 cm.$^{-1}$ (NH group?) in addition to bands at 1679 cm.$^{-1}$ (conjugated carbonyl group) and 1643 cm.$^{-1}$ (C=C). A *picrolonate* separated from methanol in brownish-yellow prisms, m. p. 136° (Found: C, 54·5;

[25] Cf. Eccott and Linstead, *J.*, 1930, 917.
[27] Marchant and Pinder, *J.*, 1956, 327.
[28] Myers, Collett, and Lazzell, *J. Phys. Chem.*, 1952, **56**, 461; Schlichting and Klager, U.S.P. 2,340,701/1944.
[29] Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.

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H, 6·4. $C_{19}H_{25}O_4N_5$ requires C, 54·5; H, 6·0%) which depressed the m. p. of the above picrolonate on admixture. Similar results were obtained when the alcohol was shaken with manganese dioxide [30] under a variety of conditions.

*4-Diethylamino-1-phenylbut-2-yn-1-ol.*—1-Phenylprop-2-ynyl acetate [31] (15·0 g.), diethylamine (7·85 g.), paraformaldehyde (2·6 g.), and dioxan (40 c.c.) were heated on the water-bath for 24 hr.[32] The solvent was evaporated under reduced pressure, the residue rendered acid with dilute hydrochloric acid, and neutral matter removed with ether. Basification with potassium carbonate and extraction with ether then gave *1-acetoxy-4-diethylamino-1-phenylbut-2-yne*, b. p. 128°/0·25 mm. (16·9 g.) (Found: C, 73·9; H, 8·2. $C_{16}H_{21}O_2N$ requires C, 74·1; H, 8·1%). Hydrolysis of the ester (13·2 g.) in methanol (50 c.c.) with 0·1M-methanolic sodium methoxide (14 c.c.) overnight at room temperature gave, after removal of the solvent and ether-extraction, *4-diethylamino-1-phenylbut-2-yn-1-ol*, which separated from light petroleum (b. p. 40—60°) in needles, m. p. 52—53° (7·8 g.) (Found: C, 76·9; H, 8·5. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8%).

*4-Diethylamino-1-phenylbut-2-en-1-ol* (XVI; R = Ph).—The above acetylenic alcohol (2·25 g.) in ethyl acetate (100 c.c.) was shaken in hydrogen at room temperature and pressure with Lindlar's catalyst [29] (0·7 g.) for 15 min. (uptake 1 mol.). The filtered solution was concentrated *in vacuo*; the residual *4-diethylamino-1-phenylbut-2-en-1-ol* distilled at 106—108°/0·15 mm. (1·93 g.) (Found: C, 76·3; H, 9·6. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6%).

Shaking the reduction product (2·0 g.) in acetone (50 c.c.) with activated manganese dioxide (5·0 g.) [30] at room temperature for 2 hr. under nitrogen gave, after filtration and concentration, a pale yellow oil, b. p. 106—108°/15 mm. (0·43 g.) (Found: C, 76·5; H, 9·5%), which could not be purified satisfactorily but evidently contained some of the desired αβ-unsaturated ketone (XI) (max. at 248 mμ; ε 2030). Infrared absorption (liquid film): bands at 1665 (cross-conjugated carbonyl group) [33] and 3130 cm.$^{-1}$ (NH group ?).

Grateful acknowledgment is made to University College, Cardiff, for the award of a research studentship (to C. B. C.). We thank Professor R. A. Raphael for arranging the ultraviolet absorption measurements (carried out by Mr. T. French), Dr. G. Eglinton for the infrared measurements, and Dr. J. W. Bayles for helpful discussion.

Queen's University, Belfast.
University College, Cardiff. [*Received, January 1st*, 1958.]

[30] Cf. Mancera, Rosenkranz, and Sondheimer, *J.*, 1953, 2189.
[31] Cf. Jones and McCombie, *J.*, 1942, 733.
[32] Cf. Jones, Marszak, and Bader, *J.*, 1947, 1578.
[33] Bellamy, " The Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 114.

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## 401. *Some 2-Substituted Linear Naphthiminazoles.*

By D. J. Brown.

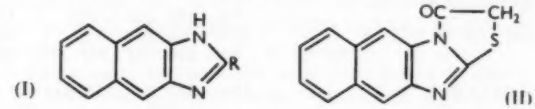
Several 2-substituted linear naphthiminazoles have been prepared; in their ionization and ultraviolet spectra the linear and the angular naphthiminazoles are shown to form a graded series with glyoxaline and benziminazole.

The scanty literature [1] of the angular (or αβ-) and the linear (or ββ-)naphthiminazoles (I; R = H) reveals that only two monosubstituted derivatives [2,3] are known in the linear series, and no spectra are recorded. To remedy this, some 2-substituted members have been prepared and their $pK_a$ values and ultraviolet spectra determined.

When 2 : 3-diaminonaphthalene was fused with urea, 2-hydroxynaphth[2,3]iminazole (I; R = OH) resulted, but phosphoryl chloride did not yield the 2-chloro-derivative from it. A similar fusion with thiourea produced 2-mercaptonaphth[2,3]iminazole which on methylation gave the methylthio-derivative. This reacted with benzylamine,

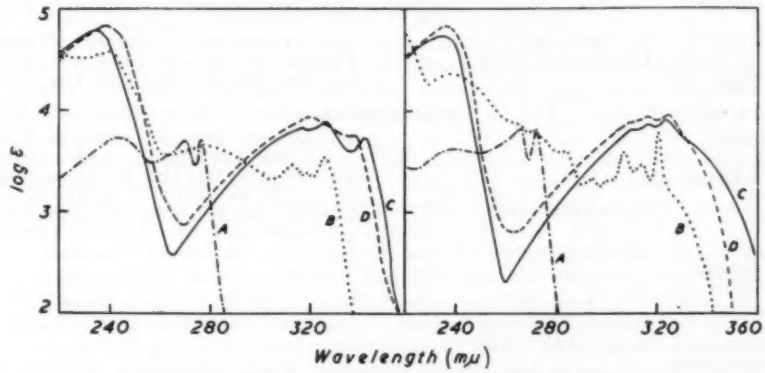
[1] Cf. Brown in the Symposium Report, " Current Trends in Heterocyclic Chemistry," Butterworths, London, 1958, p. 75.
[2] Fries, Walter, and Schilling, *Annalen*, 1935, **516**, 248.
[3] Goldstein and Streuli, *Helv. Chim. Acta*, 1937, **20**, 520.

aniline, and, more slowly, benzylmethylamine, to give respectively 2-benzylamino-, anilino-, and benzylmethylamino-derivatives. It did not react however in the same way with ammonia, methylamine, or ethylamine at the same temperature (sealed tubes), and above 180° it was destroyed by these reagents. It has been suggested [4] that this lack




of reactivity might be due to deprotonation at $N_{(1)}$ by these stronger bases, but a solution of methylamine buffered at pH 9 also did not react. The 2-amino-derivative was finally prepared by the action of cyanogen bromide on 2 : 3-diaminonaphthalene, by analogy with an example in the angular series.[5] Although 2-methylthiobenziminazole has been oxidised to the sulphone [6] 2-methylthionaphth[2,3]iminazole under similar conditions gave no isolable product. The 2-mercapto-compound with chloroacetic acid gave a

FIG. 1. FIG. 2.




*Absorption*: FIG. 1, *as neutral molecules*; FIG. 2, *as cations*.
*A, Benziminazole; B, naphth*[1,2]*iminazole; C, naphth*[2,3]*iminazole; D, 2-ethylnaphth*[2,3]*iminazole.*

carboxymethylthio-derivative (I; R = $S{\cdot}CH_2{\cdot}CO_2H$), which with acetic anhydride produced the cyclic amide (II) analogous to that described in the benziminazole series.[7]

Progressive annelation of glyoxaline weakens the basic properties, as would be expected. The basic $pK_a$ of glyoxaline [8] (7·03) is decreased by addition of a benzene ring [9] to 5·53 in benziminazole, and again for linear (5·24) and angular naphthiminazole (5·28). Similarly, that of 2-aminobenziminazole [9] is 7·54, and of the corresponding linear naphthiminazole is 7·01. The feeble acidity ($pK_a$ 14·5) of glyoxaline [10] is increased as expected by annelation (benziminazole: 13·2 *), and the naphthiminazoles are stronger acids (12·52; 12·54). With the 2-hydroxy- and the mercapto-derivative, the change from one to two benzene rings is also acid-strengthening. Alkyl groups have the usual base-strengthening and acid-weakening effects on linear naphthiminazole (cf. Table).

The ultraviolet spectra recorded in the Table form an extension to those of glyoxaline

* The earlier potentiometric figure [9] is considered to be less accurate than this spectroscopic value (see Table).

[4] *Op. cit.*, p. 79.
[5] Crippa and Maffei, *Gazzetta*, 1941, **71**, 418.
[6] Hoggarth, *J.*, 1949, 3311.
[7] Duffin and Kendall, *J.*, 1956, 361.
[8] Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146.
[9] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[10] Walba and Isensee, *J. Org. Chem.*, 1956, **21**, 702.

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| Naphth[2,3]-iminazole derivative | p$K_a$ (20°) and concn. ($10^{-5}$M) in brackets | Solubility in water at 20°; 1 in | Ultraviolet spectra in water | | |
|---|---|---|---|---|---|
| | | | pH | $\lambda_{max.}$ (mμ) | log $\varepsilon_{max.}$ |
| Unsubst.[a] | — | 5500 | 7·35 | 342; 327; 317; 235 | 3·74; 3·88; 3·83; 4·79 |
| cation | 5·24 (±0·01) [d] [100] | — | 2·0 | 325; 318; 235 | 3·90; 3·84; 4·75 |
| anion | 12·52 (±0·02) [e] [5] | — | — | — | — |
| 2-Mercapto | — | — | 6·0 | 343; 328 [b]; 272 | 4·57; 4·25; 4·81 |
| anion | 9·84 (±0·04) [e]; [1·25] | — | 12·0 | 346; 272 | 4·34; 4·76 |
| 2-Hydroxy [c] | — | $3·4 \times 10^5$ | 6·04 | 330; 315; 301; 295; 240 | 3·93; 3·74; 3·75; 3·76; 4·82 |
| anion | 11·62 (±0·01) [e] [1·25] | — | 13·0 | 337; 329; 326; 314 [b]; 249 | 3·93; 3·87; 3·86; 3·79; 4·79 |
| 2-Amino | — | 8500 | 9·2 | 334; 320; 310; 247 | 3·94; 3·89; 3·86; 4·80 |
| cation [h] | 7·01 (±0·02) [d] (100) | — | 4·9 | 328; 320; 313; 306; 300; 287 [b]; 241 | 3·98; 3·74; 3·85; 3·78; 3·84; 3·67; 4·82 |
| anion | 12·8 [e] (10) | — | — | — | — |
| 2-Methyl [a] | — | 51,000 | 9·0 | 337 [b]; 320; 237 | 3·76; 3·91; 4·81 |
| cation | 6·11 (±0·02) [d] [25] | — | 2·0 | 326; 318; 236 | 3·93; 3·91; 4·79 |
| anion | 12·9 [e] [5] | — | — | — | — |
| 2-Ethyl | — | 62,000 | 9·0 | 338; 321; 239 | 3·76; 3·92; 4·84 |
| cation | 6·14 (±0·03) [d] [25] | — | 2·0 | 326; 318; 237 | 3·95; 3·92; 4·82 |
| anion | 12·9 [e] [20] | — | — | — | — |
| 2-Carboxymethyl-thio | — | 44,000 | 3·14 [f] | 335; 326; 263 | 4·28; 4·19; 4·73 |
| cation | 1·9 [e] [1·25] | — | — | 334; 326; 261 | 4·26; 4·16; 4·73 |
| anion | 4·68 (±0·07) [e] [1·25] | — | 7·36 | 338; 327; 263; 223 | 4·19; 4·16; 4·72; 4·54 |
| 2-Methylthio | — | — | 8·0 | 338; 326; 262; 223 | 4·09; 4·04; 4·67; 4·42 |
| *Other compounds* | | | | | |
| Cyclic amide (II) | — | — | 8·0 | 337; 332; 328; 320; 315; 263; 225 | 4·19; 4·11; 4·16; 4·09; 4·03; 4·74; 4·55 |
| Naphth[1,2]imin-azole [g] | — | — | 9·2 | 326; 319; 313; 279; 273; 240; 222 | 3·54; 3·38; 3·46; 3·65; 3·63; 4·57, 4·54 |
| cation | 5·28 (±0·02) [d] (100) | — | 2·0 | 322; 315; 308; 295; 284 [b]; 273; 240 | 3·76; 3·46; 3·58; 3·32; 3·57; 3·78; 4·37 |
| anion | 12·54 (±0·04) [e] [5] | — | — | — | — |
| 2-Hydroxybenz-iminazole | — | — | — | — | — |
| cation | −1·7 [e] [10] | — | — | — | — |
| anion | 11·95 (±0·02) [e] [10] | — | — | — | — |
| 2-Mercaptobenz-iminazole (anion) | 10·24 (±0·02) [e] [1·25] | — | — | — | — |
| Benziminazole (anion) | 13·2 [e] [10] | — | — | see Figures [j] | — |

[a] Prep.: see ref. 2. [b] Shoulder. [c] Cationic p$K_a$ is <0. [d] Potentiometric titration. [e] Spectroscopic determination. [f] Mainly neutral molecule. [g] Prep.: Fischer, *J. prakt. Chem.*, 1922, **104**, 118. [h] Dicationic p$K_a$ is <1. [j] Curves constructed from Mason, *J.*, 1954, 2071, and personal communication.

and benziminazole. Thus there is a considerable bathochromic shift of the long-wavelength band (neutral molecule and cation) on passing from benziminazole to angular naphthiminazole and still more to the linear isomer and its alkyl derivatives (cf. Figures). Fine structure also increases with complexity of the ring system and naturally in this respect the unsymmetrical angular shows more than does the linear isomer. The same shift and increase in fine structure are true of the amide (II) in comparison with its benzo-analogue.[7] In the linear series the rule [11] holds good: the spectrum of the hydroxy-anion is almost identical with that of the neutral molecule of the corresponding amino-derivative (cf. Table). Likewise the anion of the carboxymethylthio- closely resembles its parent methylthio-derivative.

When viewed on a paper chromatogram in ultraviolet light, 2-mercaptonaphth[2,3]-iminazole shows a brilliant yellow phosphorescence for several seconds after withdrawal of the light source. 2-Mercaptobenziminazole does not do this.

2-Aminonaphth[2,3]iminazole showed slight antibacterial activity against *Strep. pyogenes*, *Staph. aureus*, *E. coli*, and *Pr. vulgaris* (kindly tested by Professor S. D. Rubbo, University of Melbourne).

[11] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.

## Experimental

*2-Hydroxynaphth*[2,3]*iminazole.*—2 : 3-Diaminonaphthalene (10 g.) and urea (10 g.) were heated at 180°. After 5 min. the mass solidified and after a further 5 min. it was cooled, triturated with water (25 ml.), and adjusted to pH *ca.* 5, and the solid was filtered off (11·2 g.). Recrystallization from pentyl alcohol (1500 ml.) gave colourless plates of the *hydroxy-compound* (8·5 g.), m. p. <320° (Found, in sample dried at 140°: C, 72·2; H, 4·4; N, 15·05. $C_{11}H_8ON_2$ requires C, 71·7; H, 4·35; N, 15·2%).

*2-Mercaptonaphth*[2,3]*iminazole.*—The crude solid from fusion as above of diaminonaphthalene and thiourea at 195° was extracted with 0·5N-sodium hydroxide (1500 ml.) at 50°. Treatment with carbon and adjustment of the warm solution to pH 4 with acetic acid gave a solid *thiol* (10 g.). It was recrystallised from ethyl acetate (50 parts) giving, after concentration, colourless crystals (6·8 g.), m. p. 305° (Found, in sample dried at 160°: C, 66·15; H, 3·8; N, 13·9. $C_{11}H_8N_2S$ requires C, 66·0; H, 4·0; N, 14·0%).

*2-Methylthionaphth*[2,3]*iminazole.*—The thiol (4·6 g.) was dissolved in 0·25N-potassium hydroxide (200 ml.) at 50°, and the solution filtered and cooled to 30°. Methyl iodide (4 ml.) was added and the mixture was vigorously shaken for 20 min. The suspension was adjusted to pH *ca.* 4, then chilled, and the solid filtered off (3·9 g.). Recrystallization twice from ethanol (80 ml.), with concentration, gave the *methylthio-derivative*, m. p. 241° (Found: C, 67·45; H, 4·45; S, 14·9. $C_{12}H_{10}N_2S$ requires C, 67·3; H, 4·7; S, 14·95%).

*2-Benzylaminonaphth*[2,3]*iminazole.*—The methylthio-derivative (0·5 g.) was heated with benzylamine (5 ml.) at 180° for 2 hr. After 24 hr. the solid was filtered off, washed with water, and dried (0·5 g.). Recrystallization from ethyl acetate (320 parts) gave the *benzylamino-compound* as needles, m. p. 246° (Found: C, 79·05; H, 5·6; N, 15·4. $C_{18}H_{15}N_3$ requires C, 79·1; H, 5·5; N, 15·4%).

*2-Benzylmethylaminonaphth*[2,3]*iminazole.*—The methylthio-derivative was heated with benzylmethylamine as above for 12 hr. Excess of amine was removed *in vacuo* at 100° and the solid after refrigeration was recrystallised from ethyl acetate. The *base* (0·1 g.) had m. p. 235° (Found: C, 78·7; H, 5·95. $C_{19}H_{17}N_3$ requires C, 79·4; H, 5·95%).

*2-Anilinonaphth*[2,3]*iminazole.*—Prepared as was the benzylamino-derivative, the crude *anilino-compound* (0·25 g.) was recrystallized from butyl acetate (140 parts), then having m. p. 284—285° (Found: C, 78·85; H, 5·15. $C_{17}H_{13}N_3$ requires C, 78·75; H, 5·05%).

*2-Carboxymethylthionaphth*[2,3]*iminazole.*—2-Mercaptonaphthiminazole (2·0 g.) and N-sodium hydroxide (10 ml.) were heated with chloroacetic acid (1·0 g.) in 2·5N-sodium hydroxide (4·0 ml.) for 2 hr., then cooled, diluted with water (10 ml.), and adjusted to pH 3 with hydrochloric acid. Recrystallization from pentyl alcohol (65 parts) gave the *acid* (1·1 g.), m. p. 208° (decomp.) (Found: N, 10·9. $C_{13}H_{10}O_2N_2S$ requires N, 10·85%).

1 : 2-*Dihydro*-1-*oxothiazolo*[2,3-a]*naphthiminazole.*—Acetic anhydride (1 ml.) was added to the above acid (1 g.). in pyridine (3 ml.). After 5 min. on the water-bath and cooling, the solid was removed, washed with ether, and recrystallized from ethanol (110 ml.), to give the colourless *amide* (0·4 g.), m. p. 236° (Found: C, 65·0; H, 3·45; N, 11·6. $C_{13}H_9ON_2S$ requires C, 65·0; H, 3·35; N, 11·65%).

*2-Aminonaphth*[2,3]*iminazole.*—Cyanogen bromide [from potassium cyanide [5] (3·3 g.)] in cold water (25 ml.) was added during 2 hr. to a stirred suspension of 2 : 3-diaminonaphthalene (7 g.) in water (130 ml.). After a further 4 hours' stirring at 20°, the mixture was set aside for 4 days. The solid was then filtered off and gave, after recrystallization from ethanol, the unchanged diamine (3·6 g.). The filtrate was made alkaline and chilled; the solid was filtered off and recrystallized from ethanol (25 parts), giving the *2-amino-derivative* (2·1 g.), m. p. 301° (decomp.) (Found: C, 72·4; H, 4·85. $C_{11}H_9N_3$ requires C, 72·1; H, 4·95%).

*2-Ethylnaphth*[2,3]*iminazole.*—Prepared similarly to the parent compound,[2,3] the *ethyl analogue* [from ethyl acetate (140 parts)] had m. p. 250° (Found: C, 79·3; H, 6·25. $C_{13}H_{12}N_2$ requires C, 79·55; H, 6·15%).

I thank Professor Harold Burton for facilities at Queen Elizabeth College where this work was started, Mr. E. P. Serjeant for the physical measurements, Dr. J. E. Fildes and Mr. D. Maguire for most of the analyses, Mr. K. Tratt for help with syntheses, and Professor Adrien Albert for his kindly advice.

Department of Medical Chemistry, Australian National University, Canberra. [*Received, January 6th*, 1958.]

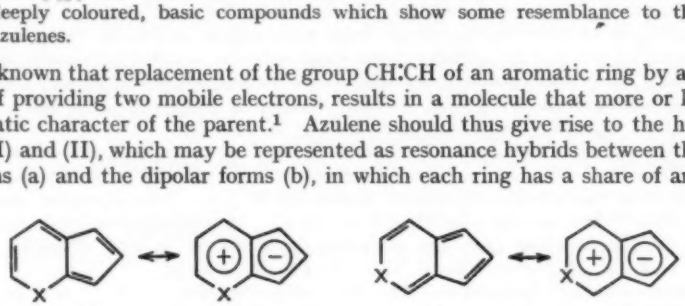
XUM

# 402. pseudo*Azulenes. Part I. Some Derivatives of* cyclo*Penta*[b]*pyran.**

By G. V. Boyd.

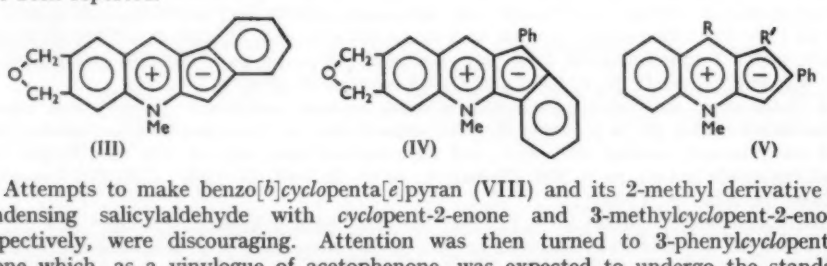
The preparation of three derivatives of the new heterocyclic system *cyclo*penta[*b*]pyran, isoelectronic with azulene, is described. These are stable, deeply coloured, basic compounds which show some resemblance to the azulenes.

It is well known that replacement of the group CH:CH of an aromatic ring by an atom X, capable of providing two mobile electrons, results in a molecule that more or less retains the aromatic character of the parent.[1] Azulene should thus give rise to the heterocyclic systems (I) and (II), which may be represented as resonance hybrids between the Kekulé-type forms (a) and the dipolar forms (b), in which each ring has a share of an aromatic sextet.



(Ia) (Ib) (IIa) (IIb)

Derivatives of the system (I; X = NMe) have been known for over thirty years, since Armit and Robinson prepared the indenoquinolines (III) [2] and (IV) [3] in order to show that aromatic character may be associated with a five-membered carbon ring in a suitable combination. In a recent Communication [4] Los, Saxena, and Stafford report the synthesis of the simpler quinindenes (V; R = H or $CO_2Me$, R′ = H or Ph), and Mayer [5] and Anderson [6] have discussed the potential aromatic character of the *cyclo*pentathiopyrans (I and II; X = S). This paper describes the preparation of three derivatives of *cyclo*penta[*b*]pyran; the synthesis of 1 : 2-diphenylbenzo[*b*]*cyclo*penta[*e*]pyran (as VIII) has just been reported.[4]



(III) (IV) (V)

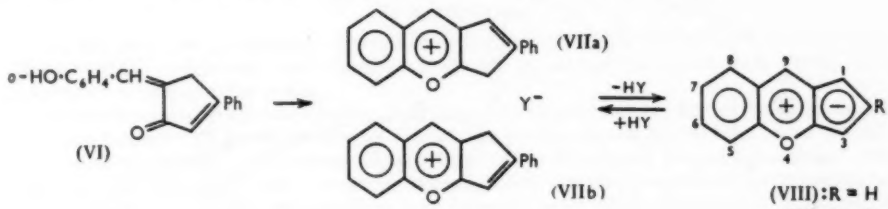
Attempts to make benzo[*b*]*cyclo*penta[*e*]pyran (VIII) and its 2-methyl derivative by condensing salicylaldehyde with *cyclo*pent-2-enone and 3-methyl*cyclo*pent-2-enone, respectively, were discouraging. Attention was then turned to 3-phenyl*cyclo*pent-2-enone which, as a vinylogue of acetophenone, was expected to undergo the standard reactions leading to benzopyrylium salts. The salicylidene derivative [7] (VI) of this ketone on being heated in acetic acid–hydrochloric acid gave a brown solution of the benzopyrylium chloride (VII; Y = Cl), from which perchloric acid precipitated the yellow perchlorate. When the brown pyrylium chloride solution was poured into water, purple 2-phenylbenzo[*b*]*cyclo*penta[*e*]pyran (IX), m. p. 207°, separated in 91% yield. It

* For preliminary account of part of this work see *Chem. and Ind.*, 1957, 1244.

[1] For a recent discussion see Baker in Todd (Ed.), "Perspectives in Organic Chemistry," Interscience Publ. Inc., London, 1956, p. 36.
[2] Armit and Robinson, *J.*, 1922, **121**, 827.
[3] *Idem, ibid.*, 1925, **127**, 1604.
[4] Los, Saxena, and Stafford, *Proc. Chem. Soc.*, 1957, 352.
[5] Mayer, *Angew. Chem.*, 1957, **69**, 481.
[6] Anderson, *Diss. Abs.*, 1957, **17**, 1210.
[7] Borsche and Menz, *Ber.*, 1908, **41**, 202.

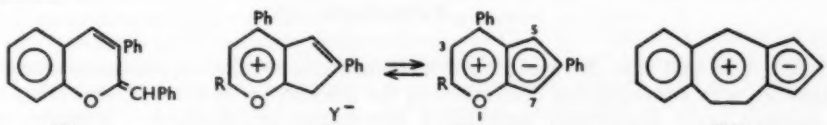
was also obtained in 41% yield by heating a benzene solution of equimolecular amounts of salicylaldehyde and 3-phenyl*cyclo*pent-2-enone for 2 hours in the presence of piperidine acetate; but in only 15% yield when 3-phenyl-5-salicylidene*cyclo*pent-2-enone was heated in benzene with the same catalyst for 21 hr. This low yield may be due to the unfavourable geometry of the salicylidene derivative.

The formulation of the purple compound as (IX) follows from its analysis, from its lack of phenolic and ketonic properties, and from its behaviour as the anhydro-base of the benzopyrylium perchlorate (VII; Y = $ClO_4$), from which it is obtained by the action of alkali or water, and into which it can be converted by treatment with perchloric acid. The constitution of the perchlorate is established by analysis and by the method of its preparation. A definite choice between the tautomeric structures (VIIa) and (VIIb) for the cation is not yet possible; but the yellow colour of the perchlorate favours the form (VIIa), since (VIIb) represents a 2-styrylbenzopyrylium perchlorate which would be expected to be red, *e.g.*, 2-3′-methoxystyrylbenzopyrylium perchlorate.[8]




2-Phenylbenzo[*b*]*cyclo*penta[*e*]pyran dissolves in organic solvents with a deep r d colour, and the solutions in concentrated hydrochloric and phosphoric acids are yellow with a faint bluish fluorescence, dilution with water regenerating the pyran. It is insoluble in, and not attacked by, boiling ethanolic potassium hydroxide; hot acetic acid decomposes it to a black tar. In its colour, basicity, and stability towards alkali, the *cyclo*pentapyran resembles the azulenes, and in the last respect differs markedly from the known quinonoid anhydro-bases of benzopyrylium salts, which are degraded by alkali. It is noteworthy that the yellow 2-benzylidene-3-phenylbenzopyran (X) also resists alkaline hydrolysis.[9]

3-Phenyl*cyclo*pent-2-enone was then used in Dilthey's pyrylium synthesis.[10] Condensation with phenyl styryl ketone in the presence of ferric chloride and acetic anhydride gave 2 : 4 : 6-triphenyl*cyclo*penta[*b*]pyrylium chloroferrate (XI; Y = $FeCl_4$) in 45% yield. This salt was converted into the yellow perchlorate, treatment of which with alkali or water yielded nearly black 2 : 4 : 6-triphenyl*cyclo*penta[*b*]pyran (XII), m. p. 148°. Similarly, from *tert.*-butyl styryl ketone the yellow perchlorate (XIII; R = $ClO_4$) and the deep purple 2-*tert.*-butyl-4 : 6-diphenyl*cyclo*penta[*b*]pyran (XIV), m. p. 136·5 — 137·5°, were obtained.




Tautomeric structures can again be written for the cations (XI) and (XIII), but the yellow colour of the perchlorates again seems to indicate the 7- rather than the 5-pyrylium

[8] Buck and Heilbron, *J.*, 1922, **121**, 1206.
[9] Dickinson, Heilbron, and O'Brien, *J.*, 1928, 2077.
[10] Dilthey, *J. prakt. Chem.*, 1916, **94**, 53.

XUM

structure (as VIIb), which would correspond to the red styrylpyrylium perchlorates, such as 2 : 4-diphenyl-6-styrylpyrylium perchlorate.[11]

The *cyclo*pentapyrans (XII) and (XIV) closely resemble the benzo-compound (IX). They are indifferent to alkali and decompose in boiling acetic acid. Solutions of their salts exhibit an intense green and blue-green fluorescence, respectively, typical of pyrylium salts. It is significant that ammonia converts the perchlorates into the corresponding *cyclo*pentapyrans and not into derivatives of pyridine, a reaction characteristic of the usual pyrylium salts.

*Spectra.*—The ultraviolet spectra of polycyclic benzenoid hydrocarbons and those of the corresponding furans, thiophens, and pyrroles have been studied by Badger and

FIG. 1. *Absorption spectra of* (*A*) 5 : 6-*benzazulene* [12] (XV) *and* (*B*) 2-*phenylbenzo*[b]cyclo*penta*[e]-*pyran* (IX).

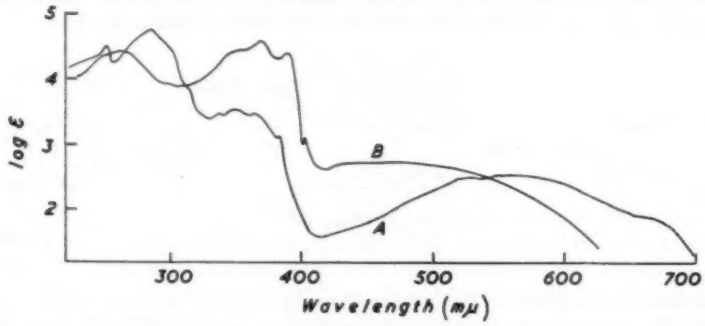
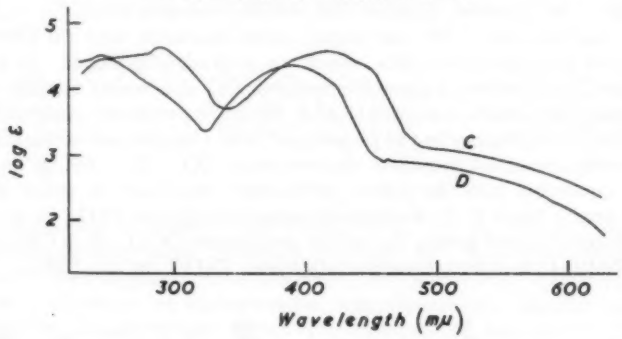



FIG. 2. *Absorption spectra of* (*C*) 2 : 4 : 6-*triphenyl*cyclo*penta*[b]*pyran* (XII) *and* (*D*) 2-tert.-*butyl*-4 : 6-*diphenyl*cyclo*penta*[b]*pyran* (XIV).




Christie,[12] who find that the spectra are fundamentally similar. A similar comparison of azulenes with corresponding derivatives of the heterocyclic systems (I) and (II) must be deferred until analogously constituted compounds are available. However, the spectrum of 2-phenylbenzo[*b*]*cyclo*penta[*e*]pyran resembles that of the unsubstituted 5 : 6-benzazulene [13] (XV) (Fig. 1), and this in turn is reported [4] to be similar to that of the corresponding nitrogen-compound (V; R = H, R′ = H). The two trisubstituted *cyclo*-pentapyrans have similar spectra (Fig. 2); substitution of the phenyl for the *tert.*-butyl group produces the expected bathochromic shift

[11] Dilthey and Fischer, *Ber.*, 1924, **57**, 1653.
[12] Badger and Christie, *J.*, 1956, 3438.
[13] Kloster-Jensen, Kováts, Eschenmoser, and Heilbronner, *Helv. Chim. Acta*, 1956, **39**, 1057.

*Ultraviolet and visible spectra.*

| Compound | Absorption max. (mμ) and log ε (in parentheses) | | | |
|---|---|---|---|---|
| 5 : 6-Benzazulene [13] (XV) (in ethanol) ..... | 252 (4·46) | 285 (4·72) | 352 (3·53) | 552 (2·51) |
| | | | 339 (3·46) | 531 (2·49) |
| | | | 364 (3·46) | 668 (1·88) |
| | | | 382 (3·11) | |
| 2-Phenylbenzo[*b*]*cyclo*penta[*e*]pyran (IX) ... | — | 260 (4·40) | 370 (4·55) | 470 (2·70) |
| | | | 346 * (4·37) | |
| | | | 364 * (4·47) | |
| | | | 389 (4·36) | |
| | | | 403 (3·09) | |
| 2 : 4 : 6-Triphenyl*cyclo*penta[*b*]pyran (XII) ... | 247 (4·49) | 290 (4·61) | 418 (4·56) | *ca.* 508 * (3·07) |
| 2-*tert.*-Butyl-4 : 6-diphenyl*cyclo*penta[*b*]pyran (XIV) ..... | | 248 (4·46) | 393 (4·34) | 462 (2·92) |

* Inflexion. Solvent, dioxan, except where otherwise stated.

## Experimental

All the pyrylium perchlorates suffered some decomposition on attempted recrystallisation. The analytical specimens were therefore prepared by adding perchloric acid (70%) to a chloroform solution of the pyran.

2-*Phenylbenzo*[b]cyclo*penta*[e]*pyran* (IX).—(*a*) A suspension of 3-phenyl-5-salicylidene-*cyclo*pent-2-enone [7] (3 g.) in acetic acid (50 ml.) and concentrated hydrochloric acid (25 ml.) was boiled for 10 min. The colour changed from red to brown and the solid dissolved. The cold solution was poured into a large volume of water, and the precipitated cyclo*pentapyran* (2·55 g., 91%), m. p. 206°, recrystallised from benzene, from which it separated in flat purple prisms, m. p. 207—207·5° (Found: C, 88·2; H, 4·5. $C_{18}H_{12}O$ requires C, 88·5; H, 4·9%).

(*b*) A solution of 3-phenyl*cyclo*pent-2-enone (158 mg.), salicylaldehyde (122 mg., 1 mol.), piperidine (2 drops), and acetic acid (1 drop) in benzene (5 ml.) was refluxed for 2 hr. On cooling, the pyran (100 mg., 41%) crystallised, having m. p. 206—207°, undepressed on admixture with the above specimen

(*c*) A suspension of 3-phenyl-5-salicylidene*cyclo*pent-2-enone (500 mg.) in benzene (25 ml.) was refluxed for 21 hr. in the presence of a small amount of piperidine and acetic acid; the clear red solution was evaporated to dryness and unchanged salicylidene compound removed by washing with aqueous sodium hydroxide; the residue (70 mg., 15%) had m. p. and mixed m. p. 207—207·5°.

The pyran was recovered after being boiled for 2 hr. with ethanolic 10% potassium hydroxide. The pyran (100 mg.) in acetic acid (5 ml.) was refluxed for 20 min.: dilution with water yielded a black tar.

2-*Phenylbenzo*[b]cyclo*penta*[e]*pyrylium perchlorate* (VII; Y = $ClO_4$), yellow, m. p. 231° (decomp. with previous darkening) (Found: C, 62·4; H, 3·7. $C_{18}H_{13}O_5Cl$ requires C, 62·7; H, 3·8%), was prepared by treating a chloroform solution of the anhydro-base with perchloric acid, or by adding perchloric acid to the brown pyrylium chloride solution prepared as in (*a*) above. Its spectrum could not be measured accurately as it decomposed too quickly in solution to the benzopyran, even in the presence of added perchloric acid. Treatment of the perchlorate with water or dilute aqueous sodium hydroxide regenerated the pyran.

2 : 4 : 6-*Triphenyl*cyclo*penta*[b]*pyrylium perchlorate* (XI; Y = $ClO_4$).—A solution of phenyl styryl ketone (6·3 g.) and 3-phenyl*cyclo*pent-2-enone (4·8 g., 1 mol.) in ether (45 ml.) and acetic anhydride (10 ml.) was slowly treated with anhydrous ferric chloride (14·7 g., 3 mol.) at 0°; the mixture was then refluxed for 1·5 hr., left overnight, and diluted with acetic acid (30 ml.); the red crude chloroferrate (XI; Y = $FeCl_4$) which separated (7·3 g., 44·7%) was washed successively with acetic acid and ether, and dissolved in warm acetone (120 ml.); addition of 70% perchloric acid (2 ml.) precipitated the yellow *pyrylium perchlorate* (5·2 g., 87%), m. p. 242° (decomp.) (Found: C, 69·4; H, 3·4. $C_{26}H_{19}O_5Cl$ requires C, 69·9; H, 4·3%), $\lambda_{max.}$ (in EtOH), 255 (log ε 4·32), 294 (4·15); 355 (4·14), 445 mμ (4·52).

The perchlorate (1·25 g.) was boiled for 10 min. with a solution of sodium hydroxide (0·8 g.) in ethanol (25 ml.) and water (2 ml.), 2 : 4 : 6-*triphenyl*cyclo*penta*[b]*pyran* (XII) (0·9 g., 93%; m. p. 147—148°) separating. The analytical sample crystallised from acetone in iodine-coloured prismatic needles, m. p. 148·5° (Found: C, 90·5; H, 5·4. $C_{26}H_{18}O$ requires C, 90·2; H, 5·2%).

The pyran was also formed when the perchlorate was treated with water or cold concentrated aqueous ammonia.

The *cyclo*pentapyran was recovered after 2 hr. in boiling ethanolic potassium hydroxide; it (100 mg.) was refluxed with acetic acid (10 ml.) for 20 min.; addition of 70% perchloric acid precipitated the perchlorate (XI; Y = $ClO_4$) (40 mg.); the filtrate gave a dark tar with water. Concentrated hydrochloric acid extracted the pyran from a chloroform solution as the sparingly soluble yellow chloride (XI; Y = Cl), which, with water, reverted to the pyran.

2-*tert.*-Butyl-4 : 6-diphenyl*cyclo*penta[*b*]pyrylium chloroferrate (28%) and *perchlorate* (XIII; Y = $ClO_4$), yellow needles, m. p. 224° (decomp.) (Found: C, 67·1; H, 5·3. $C_{24}H_{23}O_8Cl$ requires C, 67·5; H, 5·4%), $\lambda_{max.}$ (in EtOH) 274 (log ε, 3·80); 325 (4·08); 420 mμ (4·48), were similarly prepared from *tert.*-butyl styryl ketone and 3-phenyl*cyclo*pent-2-enone, but without heating of the reaction mixture. The perchlorate with water, sodium hydroxide, or aqueous ammonia gave 2-tert.-*butyl*-4 : 6-*diphenyl*cyclo*penta*[b]*pyran*, deep purple prismatic needles (from ethanol), m. p. 136·5—137·5° (Found: C, 88·5; H, 6·6. $C_{24}H_{22}O$ requires C, 88·3; H, 6·8%). This compound closely resembles the triphenyl analogue, except that it is completely decomposed after 20 min. in hot acetic acid, and its hydrochloride is quite soluble in concentrated hydrochloric acid.

WEST HAM COLLEGE OF TECHNOLOGY, LONDON, E.15. [*Received, January 8th*, 1958.]

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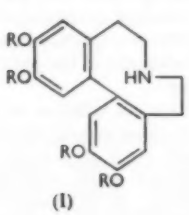
## 403. *Some Derivatives of* 3 : 4 : 3′ : 4′-*Tetramethoxydiphenyl.*

By R. I. T. CROMARTIE, JOHN HARLEY-MASON, and D. G. P. WANNIGAMA.

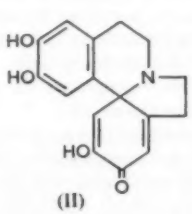
Some compounds related to 3 : 4 : 3′ : 4′-tetramethoxydiphenyl have been prepared in the course of unsuccessful attempts to obtain an azadibenzo-*cyclo*nonane as potential intermediate for synthesis of Erythrina alkaloids. A new reaction involving nucleophilic displacement of aromatic halogen, leading to dihydroindole formation, is described.

A PROJECTED synthesis in the Erythrina alkaloid field envisaged oxidation of the azadibenzo*cyclo*nonane (I; R = H) to the tetracylic system (II), following a possible biogenetic route. However, we failed to obtain the starting material (I). In this paper various intermediates prepared are described.

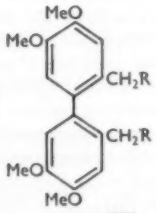
Attention was first directed to the synthesis of 4 : 5 : 4′ : 5′-tetramethoxydiphenyl-2 : 2′-diacetic acid (III; R = $CO_2H$) in the hope of subsequently obtaining the cyclic imide which might later be reduced. Iodination of 4 : 5-dimethoxyphenylacetic acid gave the 2-iodo-derivative whose ester was converted by the Ullmann reaction into the diphenyl derivative (III; R = $CO_2Me$). The free acid and diamide were readily obtained,



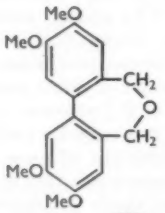
(I)



(II)



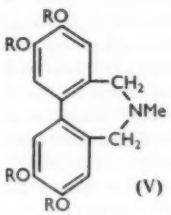
(III)



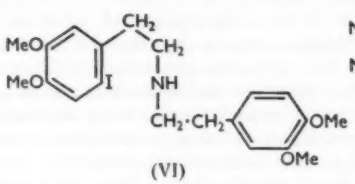
(IV)

but attempts to prepare the imide were unsuccessful. Reduction of the diester by lithium aluminium hydride gave the diol (III; R = $CH_2$·OH) but, unexpectedly, attempts to replace the hydroxyl groups by halogen failed. In another approach, 2-iodo-4 : 5-dimethoxytoluene, obtained by iodination of 4-methylveratrole with iodine monochloride, gave 4 : 5 : 4′ : 5′-tetramethoxy-2 : 2′-dimethyldiphenyl (III; R = H) by the Ullmann reaction, and this with *N*-bromosuccinimide gave the dibromo-derivative (III; R = Br).

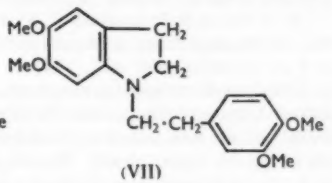
The halogen atoms in this compound were very labile: boiling the compound with methanol rapidly gave the ether (III; R = OMe), and aqueous-alcoholic potassium cyanide the dinitrile (III; R = CN), together with a small amount of the oxepin [1] (IV).



(V)



(VI)



(VII)

The oxepin was obtained in higher yield when the dibromide was treated with sodium hydroxide. It was hoped that reduction of the dinitrile would give the amine (I; R = Me) as one of the products, but none of it was isolated even by hydrogenation over Raney nickel conducted in very dilute solutions in order to favour intramolecular reaction.

The dibromo-compound (III; R = Br) reacted readily with methylamine, giving the azepine [1] (V; R = Me), demethylated by hydrobromic acid to the tetrahydroxy-compound (V; R = H), illustrating the ease of formation of a seven-membered ring in this series in contrast to the difficulty of obtaining the desired nine-membered ring.

Hydrogenation of 3 : 4-dimethoxyphenylacetonitrile over Raney nickel gave a mixture of about equal amounts of 3 : 4-dimethoxyphenethylamine and bis-3 : 4-dimethoxyphenethylamine, easily separated by distillation. Iodination of the secondary amine was examined with a view to subsequent intramolecular Ullmann reaction. A mono- and a di-iodo-derivative were obtained by treatment with iodine monochloride. The free bases were unstable, rapidly liberating iodide on storage. When the monoiodo-compound (VI) was liberated from its stable hydrochloride and taken up in benzene, the solution soon deposited crystals of the hydriodide of an iodine-free base, further characterised as picrate. Evidently cyclisation had occurred, giving the dihydroindole (VII). This ready displacement of nuclear halogen is noteworthy.

To obviate this cyclisation, the stable *N*-benzenesulphonyl derivative of the di-iodo-amine was prepared, but attempted Ullmann reactions under a variety of conditions gave none of the desired product.

## Experimental

*2-Iodo-4 : 5-dimethoxyphenylacetic Acid.*—A solution of 3 : 4-dimethoxyphenylacetic acid (75 g.) and iodine monochloride (75 g.) in acetic acid (900 ml.) was kept at room temperature for a week. Addition of water (1·5 l.) precipitated the product (90 g.) which was collected and washed with sodium thiosulphate solution. Recrystallised from aqueous ethanol, the *iodo-acid* formed colourless needles, m. p. 164—165° (Found: C, 37·8; H, 3·8. $C_{10}H_{11}O_4I$ requires C, 37·3; H, 3·4%). With refluxing, absolute methanol containing a little concentrated sulphuric acid, it gave the *methyl ester*, needles, m. p. 72—73° (from aqueous methanol) (Found: C, 39·3; H, 4·3. $C_{11}H_{13}O_4I$ requires C, 39·3; H, 3·9%).

*Dimethyl 4 : 5 : 4′ : 5′-Tetramethoxydiphenyl-2 : 2′-diacetate.*—The above ester (5 g.) and copper bronze (30 g.) were slowly heated to 200—220° and kept at that temperature for 2 hr. with occasional stirring, then cooled and extracted (Soxhlet) for 24 hr. with boiling benzene. Removal of the benzene left a dark oil, which on two recrystallisations from ethanol (charcoal) gave *dimethyl 4 : 5 : 4′ : 5′-tetramethoxydiphenyl-2 : 2′-diacetate* (1·2 g.) as rods, m. p. 145° (Found: C, 63·6; H, 6·3. $C_{22}H_{26}O_8$ requires C, 63·2; H, 6·1%). Hydrolysis with boiling aqueous sodium hydroxide gave the corresponding *acid* which formed needles, m. p. 228—230°, from aqueous ethanol (Found: C, 61·8; H, 6·2. $C_{20}H_{22}O_8$ requires C, 61·5; H, 5·7%).

The acid (3 g.) was refluxed with thionyl chloride (5 ml.) until all was dissolved (10—15 min.), and the excess of thionyl chloride was then removed under reduced pressure, leaving

[1] Cf. Beaven, Hall, Lesslie, Turner, and Bird, *J.*, 1954, 131.

crystalline acid chloride. This was triturated in small portions with ammonia solution (50 ml.; *d* 0·88) in a mortar. The resulting *diamide* was collected, washed, and recrystallised from ethanol as prisms, m. p. 233—234° (Found: C, 61·7; H, 6·7; N, 6·8. $C_{20}H_{24}O_6N_2$ requires C, 61·9; H, 6·2; N, 7·2%).

2 : 2′-*Di*-(2-*hydroxyethyl*)-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl.*—The foregoing ester (3·35 g.) was extracted from a Soxhlet thimble into a solution of lithium aluminium hydride (1·5 g.) in ether (200 ml.). When the extraction was complete (about 10 hr.), the excess of hydride was destroyed by moist ether, and dilute sulphuric acid was added to dissolve inorganic material, leaving the product (which was very sparingly soluble in ether) as a white suspension. Ethyl acetate was added until all had dissolved, the aqueous layer was separated and discarded, the organic layer dried ($Na_2SO_4$), and the solvent removed. 2 : 2′-*Di*-(2-*hydroxyethyl*)-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl* formed rhombs, m. p. 148—149·5°, from ethyl acetate–light petroleum (Found: C, 66·3; H, 7·6. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%).

4 : 5 : 4′ : 5′-*Tetramethoxy*-2 : 2′-*dimethyldiphenyl.*—3 : 4-Dimethoxytoluene (35 g.) in acetic acid (110 ml.) was treated with iodine monochloride (50 g.) in acetic acid (110 ml.). Next morning the mixture was poured into water (1·5 l.) and sulphur dioxide passed into it. The dark solid was collected and recrystallised from aqueous methanol. 2-*Iodo*-4 : 5-*dimethoxytoluene* (54 g., 85%) formed plates, m. p. 64° (Found: C, 39·1; H, 4·1. $C_9H_{11}O_2I$ requires C, 38·9; H, 4·0%). The iodo-compound (4 g.) and copper bronze (4 g.) were heated at 200—210° for 1·5 hr. The product was sublimed out of the resulting mass at 200°/1 mm., giving 4 : 5 : 4′ : 5′-*tetramethoxy*-2 : 2′-*dimethyldiphenyl* (1·2 g.), white plates, m. p. 115—116° (from aqueous methanol) (Found: C, 71·4; H, 7·2. $C_{16}H_{22}O_6$ requires C, 71·5; H, 7·3%).

2 : 2′-*Bisbromomethyl*-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl.*—To a solution of the foregoing diphenyl (1·2 g.) in dry carbon tetrachloride (20 ml.), *N*-bromosuccinimide (1·4 g.) and benzoyl peroxide (0·05 g.) were added, and the mixture refluxed for 4 hr. After filtration from succinimide, the solvent was removed, leaving brown crystals. Recrystallisation from ethyl acetate gave 2 : 2′-*bisbromomethyl*-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl* (1·2 g., 65%) as hexagonal plates, m. p. 179—180° (Found: C, 47·1; H, 4·6. $C_{18}H_{20}O_4Br_2$ requires C, 47·0; H, 4·4%). An alcoholic solution gave an immediate precipitate of silver bromide on treatment with silver nitrate. When a methanol solution of the dibromo-compound was refluxed for 1 hr. and then concentrated, 2 : 2′-*dimethoxymethyl*-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl* separated as needles, m. p. 110° (Found: C, 66·6; H, 7·4. $C_{20}H_{26}O_6$ requires C, 66·3; H, 7·2%).

The dibromo-compound (1·8 g.) was refluxed for 2 hr. with sodium hydroxide (3 g.) in water (15 ml.) and ethanol (5 ml.). After cooling and dilution with water, the pale orange solid was filtered off and recrystallised from benzene, giving 2 : 7-*dihydro*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-3 : 4-5 : 6-*dibenzoxepin* (IV) as plates m. p. 249° (Found: C, 68·2; H, 6·0. $C_{18}H_{20}O_5$ requires C, 68·6; H, 6·3%).

2 : 7-*Dihydro*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine.*—To a solution of the foregoing dibromo-compound (14·8 g.) in dry benzene (100 ml.) a solution of methylamine (3 g.) in dry benzene (100 ml.) was added and the mixture set aside overnight. The methylamine hydrobromide which had separated was filtered off and the filtrate washed with water (to remove methylamine) and extracted with dilute hydrochloric acid. The acid extract was basified by ammonia and extracted with benzene. After separation and drying ($Na_2SO_4$), the benzene was removed, leaving the crude solid amine (5·3 g., 53%). Sublimation at 120—125°/0·02 mm. gave 2 : 7-*dihydro*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine* (V; R = Me) as needles, m. p. 160—162° (Found: N, 4·2. $C_{19}H_{23}O_4N$ requires N, 4·3%). The *picrate* formed yellow needles, m. p. 211—213°, from ethanol (Found: C, 54·0; H, 4·5; N, 10·2. $C_{19}H_{23}O_4N,C_6H_3O_7N_3$ requires C, 54·0; H, 4·7; N, 10·0%). The *methiodide* formed needles, m. p. 277—278° (decomp.), from ethanol (Found: C, 51·1; H, 5·5. $C_{19}H_{23}O_4N,CH_3I$ requires C, 51·0; H, 5·5%).

The azepine (4 g.) was refluxed for 1·5 hr. with hydrobromic acid (*d* 1·49; 20 ml.). The resulting solution was evaporated to dryness under reduced pressure and the residual solid recrystallised from acetone (charcoal), giving 2 : 7-*dihydro*-2′ : 3′ : 2″ : 3″-*tetrahydroxy*-1-*methyl*-3 : 4-5 : 6-*dibenzazepine hydrobromide* as prisms, m. p. 170—172° (Found: C, 48·8; H, 5·1; N, 4·1. $C_{15}H_{15}O_4N,HBr,H_2O$ requires C, 48·5; H, 4·7; N, 3·8%).

2 : 2′-*Biscyanomethyl*-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl.*—A solution of the foregoing dibromo-compound (4·2 g.) and potassium cyanide (16 g.) in ethanol (80 ml.) and water (20 ml.) was boiled under reflux for 1·5 hr. After evaporation of the ethanol the brown tarry residue

was taken up in ethyl acetate, washed with dilute hydrochloric acid and then with water, and dried ($CaCl_2$). The solvent was removed, leaving a brown gum which crystallised on addition of methanol. Two recrystallisations from methanol gave 2 : 2-*biscyanomethyl*-4 : 5 : 4′ : 5′-*tetramethoxydiphenyl* (1·5 g.) as needles, m. p. 163° (Found: C, 67·9; H, 5·9; N, 8·0. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7; N, 8·0%).

During the recrystallisation a sparingly soluble by-product was obtained in small amount. This was shown (mixed m. p.) to be the oxepin.

*Bis*-3 : 4-*dimethoxyphenethylamine*.—A solution of 3 : 4-dimethoxyphenylacetonitrile (50 g.) in ethanol (500 ml.) was hydrogenated over Raney nickel at 80 atm. at 90° for 5 hr. After filtration the solvent was removed and then 3 : 4-dimethoxyphenethylamine (23 g.) was distilled off at 118—120°/1·5 mm. The residual oil was dissolved in ether (50 ml.) and dry hydrogen chloride passed in. The precipitated hydrochloride was collected and recrystallised from ethanol, giving bis-3 : 4-dimethoxyphenethylamine hydrochloride (23 g.) as plates, m. p. 195—196°.

The foregoing hydrochloride (13 g.) in acetic acid (20 ml.) was treated with a solution of iodine monochloride (11 g.) in acetic acid (10 ml.). After 1 hr. the yellow crystalline precipitate was collected and twice recrystallised from ethanol, giving *di*-(6-*iodo*-3 : 4-*dimethoxyphenethyl*)-*amine hydrochloride* (15·5 g.) as yellow needles, m. p. 176—177° (Found: C, 37·2; H, 4·3. $C_{20}H_{26}O_4NCII_2$ requires C, 37·9; H, 4·2%).

2 : 3-*Dihydro*-5 : 6-*dimethoxy*-1-(3 : 4-*dimethoxyphenethyl*)*indole* (VII).—The foregoing experiment was repeated but with half of the quantity of iodine monochloride. The crude monoiodo-compound (VI) was shaken with aqueous sodium hydroxide and benzene. The benzene layer was separated and when kept for a week deposited dark crystals. On two recrystallisations from ethanol these yielded the *indole hydriodide* as pale brown needles, m. p. 194° (Found: C, 49·7; H, 5·6. $C_{20}H_{25}O_4N,HI,0{\cdot}5H_2O$ requires C, 50·0; H, 5·6%). The *picrate* formed yellow prisms, m. p. 155—156° (Found: C, 53·5; H, 5·3; N, 9·5. $C_{20}H_{25}O_4N,C_6H_3O_7N_3$ requires C, 54·5; H, 4·9; N, 9·8%).

One of us (D. G. P. W.) thanks the Government of Ceylon for the award of a Scholarship.

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## 404. *The Constituents of Natural Phenolic Resins. Part XXIV.* A Synthesis of Galgravin.*

By J. G. BLEARS and R. D. HAWORTH.

Catalytic reduction of the furan (II) yielded the tetrahydrofuran derivative (Ia), which was isomerised to galgravin (Ib) by the action of perchloric acid.

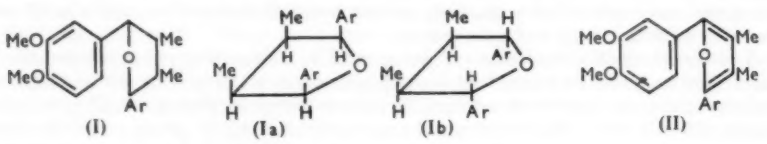
THE optically inactive lignan, galgravin, was isolated from the bark of *Himantandra belgraveana* F. Muell by Hughes and Ritchie [1] who, on the basis of degradative experiments, proposed structure (I; R = Me). Since galgravin and its derivatives are optically inactive, one of the two *meso*-forms (Ia or Ib) was considered to represent the structure of the lignan. Both these *meso*-forms have now been prepared, by catalytic hydrogenation of 2 : 5-di-(3 : 4-dimethoxyphenyl)-3 : 4-dimethylfuran [2] (II) to its tetrahydro-derivative (Ia) and subsequent isomerisation to (Ib). The latter was identical with galgravin.

Hydrogenation of the furan (II) with a palladium oxide catalyst at room temperature and atmospheric pressure gave "dimethyl dihydroguaiaretic acid" (III) as the sole product. With a palladium–charcoal catalyst, hydrogen was absorbed very slowly and, on heating, the compound (III) was again the only product. At increased pressure at room temperature, however, reaction was considerably faster and the product was an

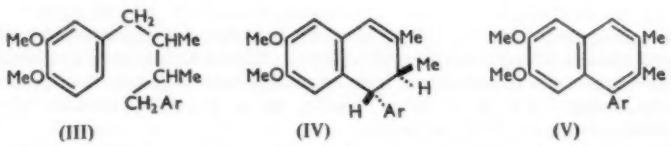
* Part XXIII, *J.*, 1955, 827.

[1] Hughes and Ritchie, *Austral. J. Chem.*, 1954, **7**, 104.
[2] Atkinson and Haworth, *J.*, 1938, 1684.

optically inactive form of the tetrahydrofuran (I), which differed from galgravin and, in accordance with Linstead's views [3,4] on the stereochemistry of catalytic hydrogenation, is considered to have the *cis*-structure (Ia). This structure is sterically more compressed than the stereoisomeric (Ib), and the possibility of isomerising it to the latter was examined.




Ar = 3:4-$(MeO)_2C_6H_3$–




Treatment of the compound (Ia) with sulphuric or perchloric acid in acetic acid for 6 days at room temperature gave *trans*-4-(3 : 4-dimethoxyphenyl)-3 : 4-dihydro-6 : 7-dimethoxy-2 : 3-dimethylnaphthalene (IV), m. p. 89—90°, which was readily reduced to the corresponding tetrahydronaphthalene derivative prepared previously by Muller and Vajda,[5] and was dehydrogenated to dimethyl dehydroguaiaretic acid (V). Hughes and Ritchie [1] found that galgravin was cyclised by acids to a dihydronaphthalene derivative, m. p. 81°, but we have repeated the experiment and find that the product has m. p. 89—90° and is identical with our specimen (IV).

When the tetrahydrofuran (Ia) was treated with perchloric acid in acetic acid for 30 min. at room temperature, it was converted in 42% yield into galgravin. The residual oil, probably a mixture of stereoisomers of galgravin, gave, on further treatment with perchloric acid in acetic acid, the dihydronaphthalene derivative (IV). In view of the ready reduction of the furan (II) to (III), the resistance to reduction reported for galgravin [1] appeared abnormal, and re-investigation has shown that galgravin is reduced in high yield to the same product (III) by hydrogen in presence of a palladium oxide catalyst.

The cyclisation and the isomerisation of the tetrahydrofuran (Ia) to the dihydronaphthalene derivative (IV) and galgravin (Ib) respectively involve the inversion of *cis*- to the more stable *trans*-structures, and the formula suggested for galgravin conforms to the usual lignan pattern derivable from two *trans*-coniferyl units.

In connection with this work, the methylenedioxy-analogues of (Ia and b), (II), and (III), together with 2 : 3-dipiperonyloylbutane have been prepared; the first two compounds represent the two *meso*-forms corresponding to the naturally occurring (—)-galbacin.[1]

## Experimental

"*Dimethyl Dihydroguaiaretic Acid*" (III).—(*a*) 2 : 5-Di-(3 : 4-dimethoxyphenyl)-3 : 4-dimethylfuran [3] (II) (100 mg.) was hydrogenated in acetic acid (50 c.c.) in presence of palladium oxide (50 mg.). Filtration and removal of the solvent under reduced pressure gave an oil which on crystallisation from methanol gave dimethyl dihydroguaiaretic acid (III), m. p. and mixed m. p. 100° (dinitro-derivative, m. p. 151—152°; dibromo-derivative, m. p. 131—132°). (*b*) Galgravin (10 mg.), treated as above, gave the same product (7 mg.), m. p. 100°.

2 : 5-*Di*-(3 : 4-*dimethoxyphenyl*)*tetrahydro*-3 : 4-*dimethylfuran* (Ia).—2 : 5-Di-(3 : 4-dimethoxyphenyl)-3 : 4-dimethylfuran (II) (150 mg.) in acetic acid–methanol (1 : 1; 150 c.c.) was hydrogenated at 30 atm. in presence of 10% palladium–charcoal (25 mg.) for 15 hr. Filtration

[3] Davies and Linstead, *J.*, 1950, 1425.
[4] Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985.
[5] Muller and Vajda, *J. Org. Chem.*, 1952, **17**, 800.

and removal of the solvent, under reduced pressure, yielded an oil which crystallised from methanol in plates, m. p. 128—130°, containing a small amount of starting material. Elution from alumina (10 g.) with benzene–ether (5 : 1) gave starting material (12 mg.) and elution with benzene–ether (3 : 2) gave 2 : 5-*di*-(3 : 4-*dimethoxyphenyl*)*tetrahydro*-3 : 4-*dimethylfuran* (105 mg.) which separated from methanol in plates, m. p. 132—133° (Found: C, 71·1; H, 7·3. $C_{22}H_{28}O_5$ requires C, 70·9; H, 7·6%). The *dinitro-derivative*, prepared in acetic acid, crystallised from methanol in pale yellow needles, m. p. 182° (Found: C, 57·1; H, 5·6; N, 6·4. $C_{22}H_{26}O_9N_2$ requires C, 57·1; H, 5·7; N, 6·1%).

trans-4-(3 : 4-*Dimethoxyphenyl*)-3 : 4-*dihydro*-6 : 7-*dimethoxy*-2 : 3-*dimethylnaphthalene* (IV).—The preceding tetrahydrofuran (100 mg.) in acetic acid (8 c.c.) containing sulphuric acid (2 drops) was kept at room temperature for 6 days, then poured into excess of dilute sodium hydroxide solution. The *product* (IV), isolated with ether, crystallised from methanol in prisms, m. p. 89—90° (Found: C, 74·5; H, 7·5. $C_{22}H_{26}O_4$ requires C, 74·5; H, 7·5%), undepressed by admixture with a specimen, m. p. 89—90°, prepared from galgravin by the same method. Reduction at atmospheric pressure and room temperature with a palladium oxide catalyst in methanol–acetic acid was complete in 2 hr.; 4-(3 : 4-dimethoxyphenyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-2 : 3-dimethylnaphthalene separated from methanol in needles, m. p. 114° (Found: C, 73·75; H, 8·0. Calc. for $C_{22}H_{28}O_4$: C, 74·1; H, 7·9%). Muller and Vajda [5] give m. p. 117°.

*Galgravin* (Ib).—2 : 5-Di-(3 : 4-dimethoxyphenyl)tetrahydro-3 : 4-dimethylfuran (50 mg.) was dissolved in acetic acid (1 c.c.) and a 10% solution (1 c.c.) of perchloric acid in acetic acid was added. After 30 min., the mixture was poured into dilute aqueous sodium hydroxide and extracted with ether. Removal of the solvent gave a colourless oil which, after two crystallisations from methanol, gave galgravin (21 mg.) as needles, m. p. and mixed m. p. 119·5°. The dinitro-derivative, prepared in acetic acid, crystallised from ethanol as pale yellow plates, m. p. and mixed m. p. 162—163°. The mother-liquors from the galgravin crystallisation yielded an oil, which, when treated as described for the preparation of the dihydronaphthalene derivative (IV), but with perchloric instead of sulphuric acid, gave the dihydronaphthalene (IV) (25 mg.), m. p. 89—90°.

2 : 3-*Dipiperonyloylbutane*.—1-α-Bromopropionyl-3 : 4-methylenedioxybenzene [6] (30 g.) was refluxed with copper powder (30 g.) in xylene (200 c.c.). After 25 hr. the solution was filtered and the solvent removed under reduced pressure. The residual *butane derivative* was obtained after several crystallisations from methanol as colourless plates (9 g.), m. p. 214—215° (Found: C, 67·7; H, 5·2. $C_{20}H_{18}O_6$ requires C, 67·8; H, 5·1%).

3 : 4-*Dimethyl*-2 : 5-*di*-(3 : 4-*methylenedioxyphenyl*)*furan*.—2 : 3-Dipiperonyloylbutane (40 mg.) was refluxed with methanol (20 c.c.) containing a few drops of concentrated hydrochloric acid. After this the solvent was removed, and the residue, crystallised first from acetic acid and then from methanol, yielded the *furan* as needles (35 mg.), m. p. 154° (Found: C, 71·4; H, 5·0. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%).

2 : 3-*Di*-(3 : 4-*methylenedioxybenzyl*)*butane*.—The preceding furan (100 mg.) was reduced as described in the preparation of " dimethyl dihydroguaiaretic acid." The product crystallised from light petroleum (b. p. 40—60°) in plates, m. p. 65—66° (lit.,[7] m. p. 70—72°). The *dibromo-derivative* crystallised from acetic acid in prisms, m. p. 136° (Found: C, 49·5; H, 4·2. $C_{20}H_{20}O_4Br_2$ requires C, 49·6; H, 4·2%).

cis-*Tetrahydro*-3 : 4-*dimethyl*-2 : 5-*di*-(3 : 4-*methylenedioxyphenyl*)*furan*, prepared in 35% yield as described above for (Ia), crystallised from methanol in needles, m. p. 94—95° (Found: C, 70·9; H, 6·4. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%). The *dinitro-derivative* crystallised from ethanol in yellow needles, m. p. 224° (Found: C, 55·5; H, 4·4. $C_{20}H_{18}O_9N_2$ requires C, 55·8; H, 4·2%).

The " trans- " *isomer*, prepared in 31% yield therefrom as described for galgravin, separated from methanol in prisms, m. p. 103° (Found: C, 70·2; H, 6·2%).

We thank Professor A. J. Birch for a sample of galgravin, the University of Sheffield for the award (to J. G. B.) of a Henry Ellison Fellowship, and Imperial Chemical Industries Limited for a grant.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, December 16th*, 1957.]

[6] Ohara, *J. Pharm. Soc. Japan*, 1951, **71**, 1244.
[7] Sugimoto and Okamura, *Chem. Abs.*, 1957, **51**, 6569.

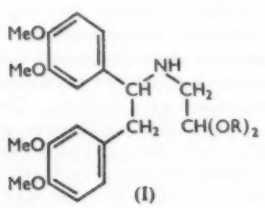
XUM

## 405. *Pavine. Part II.* The Structure of* iso*Pavine.*

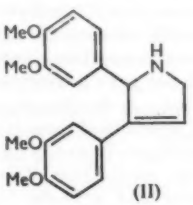
By A. R. Battersby and D. A. Yeowell.

The base obtained by acid-catalysed cyclisation of *N*-(2 : 2-dimethoxyethyl)-1 : 2-bis-(3 : 4-dimethoxyphenyl)ethylamine (I; R = Me) is shown to have the structure (IV) and is named *iso*pavine.

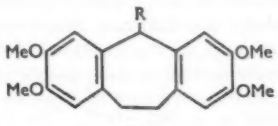
The action of concentrated sulphuric acid on the acetal (I; R = Et) has recently been shown to yield a base, $C_{20}H_{23}O_4N$, by Guthrie, Frank, and Purves.[1] These authors assigned to it the structure (II) on the basis of its mode of formation, properties, and infrared spectrum, and the fact that it differed from the dihydropapaverines and pavine.[2,3] This structure seemed unlikely to us since the methylene group attacked in its supposed formation is not sufficiently activated toward electrophilic reagents. Moreover, we had found[4] that aldehydes and acetals condense smoothly with 3 : 4 : 3′ : 4′-tetramethoxydibenzyl in the presence of sulphuric acid to give dibenz*ocyclo*heptadiene derivatives (III). The probable structure of the base $C_{20}H_{23}O_4N$ is therefore (IV), which is practically strainless on Courtauld models. Structure (IV) was one of those considered[3,5] for pavine and



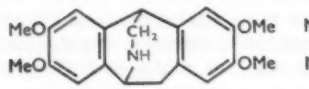

(I)



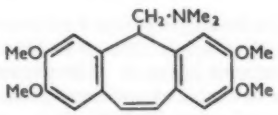

(II)



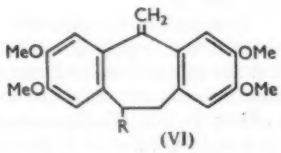

(III)




(IV)




(V)




(VI)

therefore the elucidation of the structure of the new base bears directly on our earlier work. It is convenient to name the present base *iso*pavine.

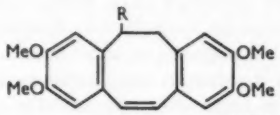
*iso*Pavine was prepared by a simplification of the original method;[1] as a by-product 3 : 4 : 3′ : 4′-tetramethoxybenzil was obtained, evidently derived from some basic intermediate (see p. 1990), but we have not investigated this aspect further. The *iso*pavine base absorbed carbon dioxide readily from the atmosphere to give a carbonate or carbamate. This unstable derivative and the base itself were readily acetylated, to yield crystalline *N*-acetyl*iso*pavine whose ultraviolet absorption corresponded to the presence of two isolated veratrole residues (see Figure); also, the acetyl derivative was unaffected by hydrogenation over platinum. These observations eliminate structure (II) for *iso*pavine.

When *iso*pavine was heated with an excess of methyl iodide, the methiodide was formed, which was smoothly degraded by Hofmann's method. On the basis of structure (IV) for *iso*pavine, the resultant *N*-methyl*iso*pavinemethine must be represented by structure (V) or (VI; R = $NMe_2$). The ultraviolet absorption of the methine supported structure (V) since the alternative structure (VI; R = $NMe_2$) would undoubtedly have ultraviolet

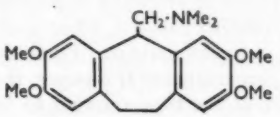
* Part I, *J.*, 1955, 2888.

[1] Guthrie, Frank, and Purves, *Canad. J. Chem.*, 1955, **33**, 729.
[2] Schöpf, *Angew. Chem.*, 1950, **62**, 453.
[3] Battersby and Binks, *J.*, 1955, 2888.
[4] *Idem*, *J.*, 1955, 2896.
[5] Schöpf, *Experientia*, 1949, **5**, 201.

absorption characteristics very similar to those of the methylenedibenzo*cyclo*heptadiene [4] (VI; R = H). In fact, the Figure shows that *N*-methyl*iso*pavinemethine has a very different absorption curve, and it also differs from the absorption curve of *N*-methylpavinemethine (VII; R = $NMe_2$). Inspection of models shows that the reason for the difference

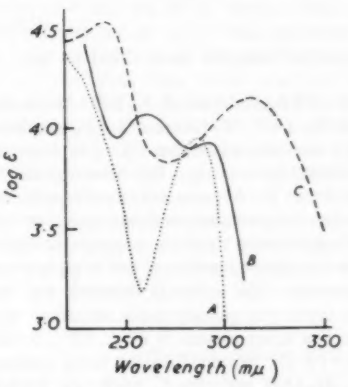



(VII)



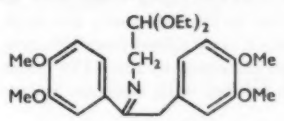

(VIII)

between the bases (VII; R = $NMe_2$) and (V) is that the aromatic rings in the former are appreciably further than in the latter from the coplanar state necessary for full interaction

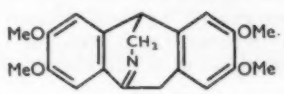



*Ultraviolet absorption spectra in ethanol of* (*A*) *N-acetylisopavine*, (*B*) *the methylenedibenzocyclo*heptadiene (VI; R = H, *and* (*C*) *N-methylisopavinemethine* (V).

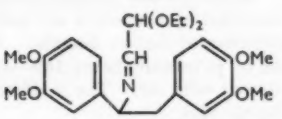
with the double bond. Further evidence in favour of structure (V) was that *N*-methyl*iso*pavinemethine methiodide was unchanged by water at 100° for 20 hr.: this stability would not be expected for the methiodide of the base (VI) since the closely related *N*-methylpavinemethine methiodide (VII; R = $^{+}NMe_3\}I^{-}$) is largely decomposed [3] under these conditions after 15 min.



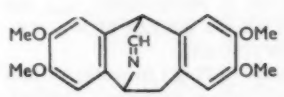

(IX)



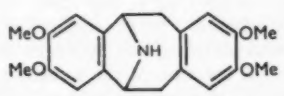

(X)



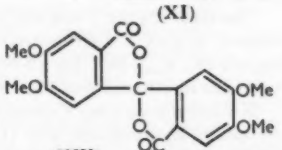

(XI)




(XII)




(XIII)




(XIV)

*N*-Methyl*iso*pavinemethine absorbed one mol. of hydrogen catalytically, the crystalline product being identical with the dibenzo*cyclo*heptadiene derivative (VIII) synthesised earlier and of fully established structure.[4] The structures of *iso*pavine and the corresponding methine are therefore established as (IV) and (V) respectively.

With the cyclisation of the acetal (I) now understood, one can consider the structure of the product, $C_{20}H_{21}O_4N$, obtained by Fritsch [6] from the similar cyclisation of the acetal

[6] Fritsch, *Annalen*, 1903, **329**, 37.

(IX), and also the nature of an isomeric base prepared by Schlitter and Müller [7] by cyclisation of the isomeric acetal (XI). The structures for these bases proposed by Guthrie *et al.*,[1] based upon (II), seem very unlikely since they are both α-pyrrolenines, the unknown tautomeric form of pyrrole. Structure (X) for Fritsch's product, based upon *iso*pavine (IV), can be rejected as sterically impossible and structure (XII) which can be considered for Schlitter and Müller's base is, when built as a model, considerably strained but probably not sufficiently so to eliminate it. Further work is required on these bases.

During the preparation of this paper, that of Waldmann and Chwala became available [8] on the structure of the base referred to here as *iso*pavine. Apparently unaware of the Canadian work,[1] they consider structures (IV) and (XIII) and select the former on the basis of the oxidation of *iso*pavine by alkaline permanganate to a crystalline product, $C_{19}H_{16}O_8$ (3—5% yield), which is assigned the structure (XIV).

## Experimental

Analytical samples were dried at 100° *in vacuo* over phosphoric oxide, unless otherwise stated.

N-(2 : 2-*Dimethoxyethyl*)-1 : 2-*bis*-(3 : 4-*dimethoxyphenyl*)*ethylamine* (I; R = Me).—A mixture of 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin (4·71 g.) and 2 : 2-dimethoxyethylamine (4·69 g.) was heated under nitrogen from 105° to 125° during 40 min., the excess of amine slowly distilling, leaving a red-brown gum (5·63 g.). This crystallised partially from methanol to give 3 : 4 : 3′ : 4′-tetramethoxydeoxybenzoin (2·4 g.), m. p. and mixed m. p. 102—103°. The mother-liquors and washings (total 50 ml.) from this crop were shaken at 20°/760 mm. with platinic oxide (0·2 g.) and hydrogen, absorption of gas (163 ml.) being complete in 3 hr. Evaporation of the filtered solution left a gum which was mainly soluble in ether; the insoluble tar was rejected. The ethereal solution was shaken with N-hydrochloric acid (24 ml.), and the aqueous layer was quickly made alkaline; the *ethylamine derivative* (I; R = Me) then separated as colourless stout prisms (1·82 g., 62% based on unrecovered starting material), m. p. 92—95°, raised to 99° by recrystallisation from methanol (Found, in material dried at 80°: C, 65·3; H, 8·0. $C_{22}H_{31}O_6N$ requires C, 65·2; H, 7·7%). The aqueous alkaline mother-liquors from the base (I; R = Me), when exposed to the air for 24 hr., deposited a further crop of yellow crystals which, purified by recrystallisation from acetic acid, had m. p. 229° (Kubiczek [9] reports m. p. 228° for 3 : 4 : 3′ : 4′-tetramethoxybenzil) (Found: C, 65·7; H, 5·9; N, 0·0. Calc. for $C_{18}H_{18}O_6$: C, 65·45; H, 5·5%), ultraviolet absorption in ethanol, $\lambda_{min.}$ 251 and 300, $\lambda_{max.}$ 230, 284, 322 mμ (log ε 3·35, 4·17, 4·37, 4·26, 4·29, respectively).

iso*Pavine and N-Acetyliso*pavine.—The foregoing acetal (1 g.) was cyclised essentially as described by Guthrie *et al.*[1] and the mixture was worked up for base in the usual way but with exclusion of carbon dioxide. A red gum (0·77 g.) was obtained which crystallised from ethanol, the m. p. initially being 149—151° (reported [1] m. p. 150—154°) but changing to 165—175° after contact with air. The material of higher m. p. effervesced when treated with aqueous hydrochloric acid.

The base (25 mg.) was acetylated in the usual way and the neutral product crystallised from ethanol, to give *N*-acetyl*iso*pavine (19 mg.), m. p. 202—203° (lit.,[1] m. p. 203·5—204°), $\lambda_{min.}$ 258 (log ε 3·18), $\lambda_{max.}$ 287 (log ε 3·95) in ethanol. No gas was absorbed when a solution of *N*-acetyl-*iso*pavine in ethanol was shaken with platinum and hydrogen at 20°/750 mm.

N-*Methyliso*pavine *Methiodide*.—A solution of the foregoing base (0·77 g.) in water (5 ml.) containing hydrochloric acid (1 equiv.) was treated with anhydrous sodium carbonate (0·98 g.), methanol (15 ml.), and methyl iodide (7 ml.). After the mixture had been heated under reflux for 9 hr., the methanol and excess of methyl iodide were evaporated, and the aqueous solution was acidified with hydrochloric acid and treated with potassium iodide (1 g.). The precipitated quaternary iodide was collected and that remaining in solution was extracted into chloroform and recovered from the dried solution by evaporation. The combined crude iodide was recrystallised (charcoal) from water by precipitation of the salt (0·85 g., 71%) with potassium iodide (3·5 g.). Recrystallisation of this *salt* twice from water and twice from methanol gave

[7] Schlittler and Müller, *Helv. Chim. Acta*, 1948, **31**, 914.
[8] Waldmann and Chwala, *Annalen*, 1957, **609**, 125.
[9] Kubiczek, *Monatsh.*, 1946, **76**, 54.

colourless prisms, m. p. 230° (decomp.) after sintering at 169° (Found: C, 52·2; H, 5·8; N, 2·8. $C_{22}H_{28}O_4NI,CH_4O$ requires C, 52·2; H, 6·1; N, 2·65%).

N-*Methyl*iso*pavinemethine* (V).—A solution of *N*-methyl*iso*pavine methiodide (0·25 g.) in warm water (10 ml.) was shaken with moist silver oxide (from 0·5 g. of silver nitrate) for 3 hr. and then filtered. The clear filtrate and washings (now 30 ml.) were treated with potassium hydroxide (30 g.) and heated under reflux for 3 hr., a crystalline precipitate being formed. This was extracted into ether and separated in the usual way into a neutral (3 mg.) and a basic fraction (0·15 g.), m. p. 157—158°. Crystallisation of the latter from ethanol gave the *methine base*, m. p. 158—159° (Found: C, 71·9; H, 7·6; N, 3·8. $C_{22}H_{27}O_4N$ requires C, 71·5; H, 7·4; N, 3·8%), ultraviolet absorption in ethanol, $\lambda_{max.}$ 239, 314; $\lambda_{min.}$ 272 (log ε 4·54, 4·15, 3·83, respectively).

N-*Methyl*iso*pavinemethine Methiodide*.—A solution of the methine (20 mg.) in ether (3 ml.) and methyl iodide (0·3 ml.) was kept overnight. Crystals separated (23 mg.), having m. p. 269° after some decomp. at 170°. These crystals were washed thoroughly with ether.

All this product was heated under reflux in water (3·5 ml.) for 20 hr. without the smell of trimethylamine being detected. The solution was then diluted to 10 ml. and extracted thrice with ether which removed a trace of brown gum. Concentration of the aqueous layer gave starting material (23 mg.) which was recrystallised several times from water to afford the pure *methine methiodide* (Found: C, 54·1; H, 5·9. $C_{23}H_{30}O_4NI$ requires C, 54·0; H, 5·9%).

*Dihydro*-N-*methyl*iso*pavinemethine* (3-*Dimethylaminomethyl*-2′ : 3′ : 2″ : 3″-*tetramethoxy*-1 : 2-4 : 5-*dibenzo*cyclo*hepta*-1 : 4-*diene* (VIII).—The methine (V) (20 mg.) was shaken with pre-reduced platinum catalyst (10 mg.) in glacial acetic acid (10 ml.) under hydrogen at 17°/761 mm. Absorption of gas (1·02 mol.) was complete in 8·5 hr. After filtration, the solution was evaporated to dryness and the residue was dissolved in aqueous hydrochloric acid. This solution was extracted thrice with ether and then basified; crystals separated (20 mg.), having m. p. 134—136°, raised to 136—138° by recrystallisation from aqueous methanol, unchanged in admixture with an authentic sample [4] of the base (VIII). The two samples of the base (VIII) had identical infrared spectra.

THE UNIVERSITY, BRISTOL. [*Received, January 30th*, 1958.]

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## 406. (—)-3α : 6β-*Ditigloyloxytropane, a New Alkaloid, from the Roots of* Datura.

By W. C. EVANS and M. WELLENDORF.

A new alkaloid isolated from the roots of *Datura innoxia* and *D. stramonium* was shown by hydrolysis to be the ditigloyl ester of (+)-tropane-3α : 6β-diol. This constitution was confirmed by comparison of the natural alkaloid with (—)-3α : 6β-ditigloyloxytropane prepared by partial synthesis.

THE roots of *Datura stramonium* L. have long been known to contain hyoscyamine [1] and more recently paper chromatography has indicated its co-occurrence with hyoscine, *apo*atropine, meteloidine, two unknown alkaloids,[2] and cuscohygrine.[3] 3 : 6-Ditigloyloxytropan-7-ol has been isolated from the weakly basic fractions of a root extract.[4] *Datura innoxia* Miller roots are reported to contain cuscohygrine,[3] hyoscyamine, hyoscine, and two uncharacterised bases.[5]

[1] Feldhaus, *Arch. Pharm.*, 1905, **243**, 328.
[2] Romeike, *Pharmazie*, 1953, **8**, 668; *Flora*, 1956, **143**, 67.
[3] Reinouts van Haga, *Nature*, 1954, **174**, 833.
[4] Evans and Partridge, *J.*, 1957, 1102.
[5] Steinegger and Gessler, *Pharm. Acta Helv.*, 1955, **30**, 279.

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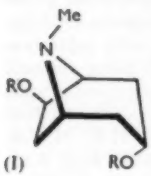
An acid solution of the total bases extracted from *D. innoxia* roots yielded to chloroform an alkaloid which was isolated as the picrate, $C_{18}H_{27}O_4N,C_6H_3O_7N_3$. From it a lævorotatory base was regenerated and this furnished a chloroplatinate, $(C_{18}H_{27}O_4N)_2,H_2PtCl_6$. An identical alkaloid was recovered from the mother-liquors of the crystallisation of 3 : 6-ditigloyloxytropan-7-ol hydrobromide [4] from a root extract of *D. stramonium*. The yield of base from the two plants was 0·001 and 0·0002% respectively.



(I)

Hydrolysis of the base with aqueous-ethanolic barium hydroxide furnished (+)-tropane-3α : 6β-diol (I; R = H) and tiglic acid. The yield of the latter indicated a ditigloyl ester (I; R = Me·CH:CMe·CO).

Hyoscine and valeroidine are both β-orientated at $C_{(6)}$ and α-orientated at $C_{(3)}$.[6,7] (±)-Tropane-3 : 6-diol obtained by hydrogenation and subsequent hydrolysis of hyoscine [6] and the (—)-isomer from the hydrolysis of valeroidine [8,9] have similar configurations. The identity of the new alkaloid with (—)-3α : 6β-ditigloyloxytropane prepared by the esterification of (+)-tropane-3α : 6β-diol with tigloyl chloride confirmed its structure. The (+)-isomer was prepared from the alkamine of valeroidine. Recrystallisation of a mixture of equal weights of the (+)- and the (—)-alkaloid picrate afforded a racemic compound of different crystalline structure from, and m. p. 24° above, the natural derivative. There were no significant differences between the infrared spectra of the natural alkaloid picrate and that of the synthesised (—)-picrate crystallised under similar conditions, when determined by the potassium chloride pressed disc technique. The differences between the infrared spectra of the similarly recrystallised (—)-, (+)-, and (±)-isomers are consistent with the general observations on the effect of spatial configuration on infrared absorption in the solid state. In this instance the differences were sufficient for the detection of partly racemised salts.

## Experimental

*Isolation of the Alkaloid Picrate.*—(i) The powdered roots of *D. innoxia* (32 kg.) were moistened with water, mixed with calcium hydroxide (1·6 kg.), and after 2 hr. exhaustively extracted by continuous percolation with industrial methylated spirit. Removal of most of the solvent from the percolate (90 l.) left a brown viscous liquid. This was rendered alkaline and the liberated bases were collected in chloroform. Neutralisation of the crude alkaloid mixture with N-sulphuric acid indicated a basic equivalent of 128 g. of hyoscyamine. The faintly acid solution of the alkaloid sulphates was filtered and repeatedly shaken with chloroform. Evaporation of the solvent afforded a brown gum, which by paper chromatography was shown to consist of alkaloids of high $R_F$ values. A neutral solution of the gum in dilute hydrochloric acid, when treated with sodium picrate solution, gave a flocculent mass which crystallised on addition of ethanol followed by warming. The solid was filtered off; then, overnight, the filtrate deposited a *picrate* which crystallised from aqueous ethanol as filamentous needles (0·02 g./kg. of root), m. p. 150—151° (Found: C, 52·5; H, 5·6; N, 10·2. $C_{18}H_{27}O_4N,C_6H_3O_7N_3$ requires C, 52·4; H, 5·5; N, 10·2%).

(ii) The mother-liquors from the crystallisation of 3 : 6-ditigloyloxytropan-7-ol hydrobromide [4] derived from the roots of *D. stramonium*, on treatment with sodium picrate, afforded a picrate (0·004 g./kg.) identical with that obtained from *D. innoxia* roots (Found: C, 52·4; H, 5·4%).

*Base and Chloroplatinate.*—A solution of the picrate in chloroform was washed with aqueous ammonia and the base recovered as a colourless gum, $[\alpha]_D^{20}$ −21·5° (*c* 3·1 in EtOH, *l* 5 cm.). The base, in dilute hydrochloric acid, furnished with chloroplatinic acid a *chloroplatinate* as

[6] Fodor and Kovács, *J.*, 1953, 2341.
[7] Fodor, Vincze, and Tóth, *Experientia*, 1957, **13**, 183; Fodor, *ibid.*, 1955, **11**, 129.
[8] Barger, Martin, and Mitchell, *J.*, 1937, 1820.
[9] Stoll, Lindenmann, and Jucker, *Helv. Chim. Acta*, 1953, **36**, 1506.

orange rosettes which crystallised from very dilute hydrochloric acid as plates, m. p. 230° (decomp.) [Found: C, 40·8; H, 5·4; Pt, 18·8. $(C_{18}H_{27}O_4N)_2,H_2PtCl_6$ requires C, 41·1; H, 5·3; N, 2·7; Pt, 18·5%].

*Hydrolysis*.—The base (0·03 g.) in ethanol (1 ml.) was refluxed with a solution of barium hydroxide (0·3 g.) in water (5 ml.) for 2 hr. The turbid suspension was washed with chloroform, and the barium removed as sulphate. From the filtrate, acidified with dilute sulphuric acid, ether removed tiglic acid (0·015 g., 79%), m. p. and mixed m. p. 62·5° (Found: C, 59·8; H, 7·8. Calc. for $C_5H_8O_2$: C, 60·0; H, 8·0%). The aqueous solution, neutralised by the addition of barium carbonate, was filtered and evaporated to dryness under reduced pressure. The residual sulphate, $[\alpha]_D^{20}$ +10·9° (*c* 1·1 in EtOH, *l* 5 cm.), was dissolved in water and with sodium picrate afforded (+)-tropane-3α : 6β-diol picrate, m. p. and mixed m. p. 249° (decomp.) [Found: C, 43·4; H, 4·7. Calc. for $C_8H_{15}O_2N,C_6H_3O_7N_3$: C, 43·5; H, 4·7%]. Fodor and Kovács [6] give m. p. 251—252° and Wolfes and Hromatka [10] m. p. 253° (decomp.) for (+)-tropane-3α : 6β-diol and Stoll, Becker, and Jucker [11] record m. p. 248° (decomp.) for the (±)-salt. The low m. p. of our (+)-salt was probably due to admixture with a small quantity of the (±)-picrate produced by the easy racemisation of the parent alkaloid.

(−)-3α : 6β-*Ditigloyloxytropane and its Derivatives*.—(+)-Tropane-3α : 6β-diol (+)-tartrate was prepared from the (±)-base by Fodor and Kovács's method.[6] Tigloyl chloride (0·14 g.) was added to the (+)-salt (0·08 g.), and the mixture kept at 105° for 3 hr., then at room temperature overnight. The unchanged tigloyl chloride was decomposed with water (5 ml.), the liberated acid removed with ether, and the alkaloid salt collected in chloroform. The residue remaining after the removal of the solvent was dissolved in water (4 ml.) and with sodium picrate furnished (−)-3α : 6β-*ditigloyloxytropane picrate* (0·08 g., 43%) as needles (from aqueous ethanol), m. p. and mixed m. p. with natural alkaloid picrate, 149° (Found: C, 52·1; H, 5·5%). The base, $[\alpha]_D^{20}$ −12·0 (*c* 2·5 in EtOH, *l* 5 cm.), liberated from the picrate solution with ammonia and collected in chloroform, was neutralised with dilute hydrochloric acid. With chloroplatinic acid it furnished a *chloroplatinate* which crystallised from very dilute hydrochloric acid as plates, m. p. 232° (decomp.) (Found: C, 41·4; H, 5·3; Pt, 18·3%).

(+)-3α : 6β-*Ditigloyloxytropane and its Derivatives*.—These were prepared in a similar way to the (−)-compounds but from the (−)-base (0·1 g.), obtained by the hydrolysis of valeroidine.[8] The *picrate* (0·07 g., 71·4%) crystallised from aqueous ethanol as needles, m. p. 151—152°, mixed m. p. with natural alkaloid picrate and synthesised (−)-alkaloid picrate, 170° (Found: C, 52·2; H, 5·4%). The base was obtained as a gum, $[\alpha]_D^{20}$ +18·6° (*c* 3·7 in EtOH, *l* 5 cm.), and the *chloroplatinate* formed plates, m. p. 230° (decomp.) (Found: C, 41·4; H, 5·6; N, 2·4; Pt, 18·8%). Equal weights of the picrate and the natural alkaloid picrate, mixed and recrystallised from aqueous ethanol, afforded prisms, m. p. 173—175°.

The infrared spectrum of the (+)-alkaloid picrate differed from that of the (−)-isomer in the following respects: a doublet at 730 and 740 cm.$^{-1}$, a shoulder at 715 cm.$^{-1}$, a sharpening of the band at 782 cm.$^{-1}$, a splitting of the band at 1133 cm.$^{-1}$, enhancement of the bands at 1228, 1342, and 3030 cm.$^{-1}$, and numerous minor differences. Differences in the spectrum of the (±)-alkaloid picrate included an enhanced band at 1026 cm.$^{-1}$, a splitting of the band at 1072 cm.$^{-1}$, and a 1133 cm.$^{-1}$ doublet.

We are indebted to Professor G. Fodor for a sample of (±)-tropane-3α : 6β-diol, to Dr. W. Mitchell and Dr. F. R. Smith for samples of valeroidine, and to Dr. M. W. Partridge for his advice and continued interest in this work. For the determination of the infrared spectra, we thank Mr. P. G. Marshall, Standards Department, Boots Pure Drug Co., Ltd.

The Department of Pharmacy, University of Nottingham. [*Received, February 3rd*, 1958.]

[10] Wolfes and Hromatka, *Ber.*, 1934, **47**, 45.
[11] Stoll, Becker, and Jucker, *Helv. Chim. Acta*, 1952, **35**, 1263.

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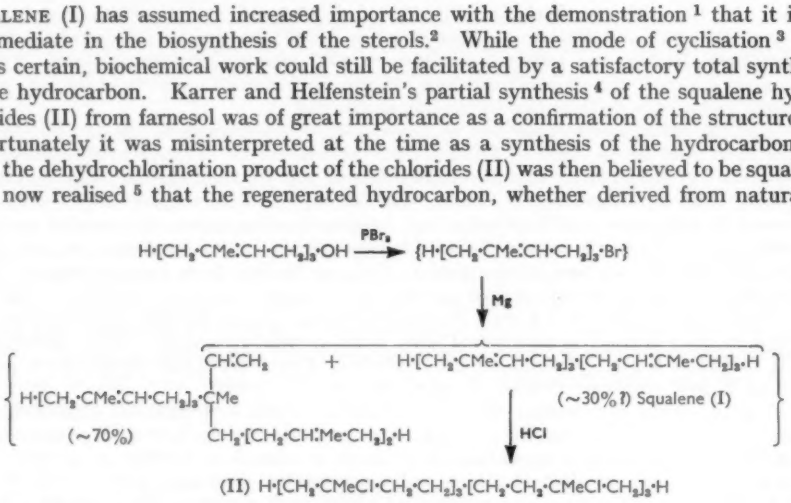
## 407. *Synthetical Studies on Terpenoids. Part I. The Synthesis of Squalene.*

By D. W. Dicker and M. C. Whiting.

General problems involved in the synthesis of squalene are discussed, earlier work is reviewed, and a method is described whereby pure squalene can be obtained synthetically by a Wittig–Schölkopf reaction between 1 : 4-dibromobutane and pure geranylacetone, followed by isolation of the all-*trans*-isomeride as its thiourea clathrate.

Squalene (I) has assumed increased importance with the demonstration [1] that it is an intermediate in the biosynthesis of the sterols.[2] While the mode of cyclisation [3] now seems certain, biochemical work could still be facilitated by a satisfactory total synthesis of the hydrocarbon. Karrer and Helfenstein's partial synthesis [4] of the squalene hydrochlorides (II) from farnesol was of great importance as a confirmation of the structure (I). Unfortunately it was misinterpreted at the time as a synthesis of the hydrocarbon (I), since the dehydrochlorination product of the chlorides (II) was then believed to be squalene. It is now realised [5] that the regenerated hydrocarbon, whether derived from natural or



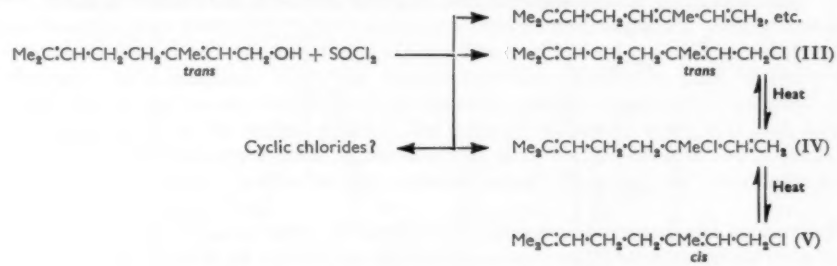

synthetic hydrochlorides, can contain, at the most, 3% of squalene (probably much less). This hydrocarbon, conveniently called "*pseudo*squalene," must consist of a mixture of all the possible products of olefin-forming eliminations, which, including stereoisomers, number 1275.*

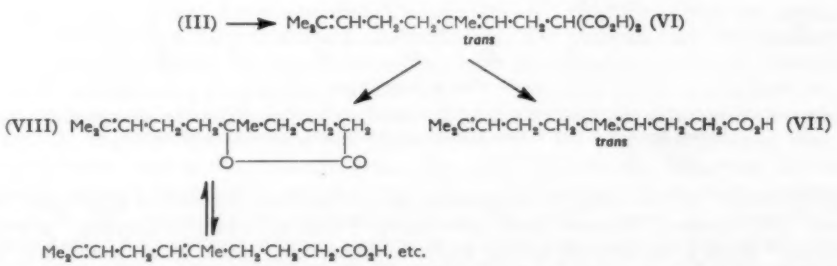
There are ten possible stereoisomers of structure (I). The formation of a thiourea adduct in high yield [6] suggests that most of the natural hydrocarbon, at least, is the all-*trans*-form. This has a shape well suited to complex formation; when Catalin models are used its dimensions are 34·4 × 6·7 × 4·65 Å, which, after correction to van der Waals radii, become about 35 × 7·3 × 5·1 Å, the width of the two farnesyl chains (which are not quite collinear) being only 6·2 Å. For adduct formation Schiessler and Flitter [7] found

* In a compound R–R′, in which R and R′ may each exist in the same $n$ forms, there exist $n$ forms in which R = R′; for each form, $R_a$, of R, there are $(n - 1)$ unsymmetrical forms (R–R′); but, since $R_a - R'_b \equiv R_b - R'_a$ (when optical isomerism is not involved), the number of unsymmetrical forms is $n(n - 1)/2$, and the total number of forms is $n(n + 1)/2$. For the farnesyl group ($2 \times 5 \times 5$) forms are possible if equilibration of double-bond isomers is permitted, and ($1 \times 2 \times 2$) if only stereoisomerism is allowed. An approximate calculation of the squalene content of the dehydrochlorination product of the squalene hexahydrochloride, based on the results of dehydrobrominating 2-bromo-2-methylbutane (Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 442), gave 0·14%.

[1] Langdon and Bloch, (*a*) *J. Amer. Chem. Soc.*, 1952, **74**, 1869; (*b*) *J. Biol. Chem.*, 1953, **200**, 135.
[2] Heilbron, Kamm, and Owens, *J.*, 1926, 1630; Channon, *Biochem. J.*, 1926, **20**, 400.
[3] Woodward and Bloch, *J. Amer. Chem. Soc.*, 1953, **75**, 2023.
[4] Karrer and Helfenstein, *Helv. Chim. Acta*, 1931, **14**, 78.
[5] Dauben, Bradlow, Freeman, Kritchevsky, and Kirk, *J. Amer. Chem. Soc.*, 1952, **74**, 4321; Tomkins, Dauben, Sheppard, and Chaikoff, *J. Biol. Chem.*, 1953, **202**, 487.
[6] Nicolaides and Laves, *J. Amer. Chem. Soc.*, 1954, **76**, 2596.
[7] Schiessler and Flitter, *ibid.*, 1952, **74**, 172.

that 5·8 × 6·8 Å was the optimal molecular cross-section; models of the 6-*cis*- and the 10-*cis*-isomer in their most stable conformations are bent, with minimal *y*-axes of 12·5 and 13 Å, respectively. The all-*cis*-isomer, with a *y*-axis of 8·4 Å, is the most nearly linear form after the all-*trans*-isomer, but even this is larger than that of any of the hydrocarbons found [7] capable of complex-formation. Nicolaides and Laves,[6] however, deduced the all-*trans*-configuration not from the mere fact that squalene formed a stable thiourea clathrate, but from the difference in *X*-ray spacing constants between the clathrates of squalene and perhydrosqualene. (This was a wise precaution in view of the fact that in urea clathrates, at least, a molecule possessing a long chain of the correct dimensions may be able to form a complex despite the presence of a " bulge " over a short distance.[7]) The numerous postulated [8] modes of cyclisation of squalene to a variety of natural terpenoids all require an all-*trans*-configuration; indeed the only real question remaining is whether any other isomer exists in the natural hydrocarbon and, if so, whether it has any biogenetic importance. Although up to a third of commercial " 90% squalene " fails to form an adduct—the yield of clathrate from squalene already purified by this method exceeds 80% under similar conditions—the non-complexed material may well consist largely of artefacts. Accordingly it seems permissible to *define* squalene as the all-*trans*-form of (I), and this definition is, in fact, implicit in some recent discussions.




The mixture of hydrocarbons from which the squalene hydrochlorides were first prepared synthetically [4] may have been quite rich in squalene. If the (naturally derived) farnesol used was the pure *trans,trans*-isomer—a point on which little definite evidence has been published—and if configuration, structural and geometrical, at the three double bonds were quantitatively retained, the $C_{30}$ fraction might have contained as much as 30% of squalene, according to the results of analogous coupling experiments on the lower isoprenoid homologues.[9] On the other hand the hydrocarbons prepared by Schmitt [10] and by Farmer and Sutton,[11] and examined by Dauben and Bradlow,[12] must have been mixtures of—on the most favourable assumptions—fifteen isomers, and their squalene

[8] Eschenmoser, Ruzicka, Jeger, and Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890.
[9] Barnard and Bateman, *J.*, 1950, 932.
[10] Schmitt, *Annalen*, 1941, **547**, 115.
[11] Farmer and Sutton, *J.*, 1942, 116.
[12] Dauben and Bradlow, *J. Amer. Chem. Soc.*, 1952, **74**, 5204.

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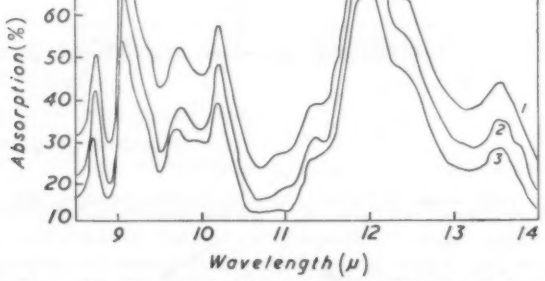
content must have been, and indeed demonstrably was,[15] very low. Trippett's synthesis,[13] similar to that described below, was thus the first preparation of a mixture of squalene stereoisomers almost uncontaminated with prototropic isomers, although as is shown below the all-*trans* content is unlikely to have greatly exceeded 25%. On the other hand, the synthesis by Isler, Rüegg, Chopard-dit-Jean, Wagner, and Bernhard,[14] which involved major modifications of the Karrer synthesis [4] and was submitted for publication very shortly after our own preliminary note,[15] did give isolable, all-*trans*-squalene.

As a starting-point for the synthesis of squalene the crystalline calcium chloride complex of geraniol has obvious advantages. Attempts to transform the pure geraniol obtained on regeneration into reactive derivatives without loss of configuration were not successful, toluene-*p*-sulphonyl chloride in pyridine giving either geranyl chloride or the pyridinium salt rather than the desired toluene-*p*-sulphonyl ester. The pyridinium toluenesulphonate proved to be very unstable and unreactive toward sodiomalonic ester. The use of a " geranyl halide " therefore seemed necessary. As previous work showed,[9] " geranyl chloride," obtained by conventional methods, is a mixture of the desired chloride (III) with " linalyl chloride " (IV), which on isomerisation or by reaction with nucleophilic

*Infrared spectra*: 1, *Squalene (natural, three times regenerated).* 2, *Squalene (synthetic, twice regenerated).* 3, *Stereoisomers of squalene unaffected by thiourea under usual conditions.*




*Spectra were determined on neat liquids in a cell of about 0·05 mm. path-length; the " percentage transmitted " values for nos. 3 and 2 have been increased by 10% and 5%, respectively.*

reagents would be converted in comparable proportions into derivatives of geraniol and nerol. Furthermore, Sörensen *et al.* have shown [16] that on reductive coupling " geranyl chloride " gives a mixture containing cyclic hydrocarbons, which in all probability are formed from cyclic contaminants in the geranyl chloride. Now, in any synthetic preparation of squalene, it was necessary to minimise the formation of isomeric, including stereoisomeric, hydrocarbons, which would interfere with the formation of the squalene–thiourea clathrate; and the 6-*cis*-isomer was a particularly dangerous contaminant because of the possibility that it might form a (less stable) clathrate itself, having, for much of its length, the correct molecular cross-section. In any synthesis from geranyl chloride, a further crystalline intermediate was therefore considered essential. Geranylmalonic acid, not previously described, and geranylacetone semicarbazone were obvious possibilities.

Geranyl chloride was chosen in preference to the bromide because of the probability that the latter, but not the former, would equilibrate with its anionotropic isomers at room

[13] Trippett, *Chem. and Ind.*, 1956, 60.
[14] Isler, Ruegg, Chopard-dit-Jean, Wagner, and Bernhard, *Helv. Chim. Acta*, 1956, **39**, 879.
[15] Dicker and Whiting, *Chem. and Ind.*, 1956, 351.
[16] N. A. Sørensen, Gillebo, Holtermann, and J. S. Sørensen, *Acta Chem. Scand.*, 1951, **5**, 757.

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temperature.[17] In the halogenation much hydrocarbon (presumably myrcene and ocimene, although cyclic products may also be present) is formed concurrently; to separate the chloride, distillation has been customary. Indeed Barnard and Bateman [9] say that, on heating, " a more homogeneous product " results, implying that the equilibration of the three chlorides gives a mixture containing less of the tertiary isomer than does the product of the kinetically controlled reaction. This, however, must mean the formation of a large proportion—probably nearly 50%—of the *cis*-isomer (V). We therefore chose to treat the crude, undistilled chloride–hydrocarbon mixture with sodio-malonic or -acetoacetic ester solutions, and distil the stable products (after hydrolysis to geranylacetone in the latter case).

Geranylmalonic ester has been prepared before, but gave a syrupy acid on hydrolysis.[18,19] Our specimen was hydrolysed to an acid which solidified on cooling; about a third could be obtained crystalline, and when pure it melted at 50·5—51·5°. The low yield from constant-boiling ester reveals the presence of isomeric impurities in the latter, although no doubt they amounted to much less than two-thirds of the whole product; the non-crystalline acid in the mother-liquors had an infrared spectrum not greatly different from that of the crystalline product, which at least excluded the presence of $H_2C{=}C<$ groupings. The crystalline acid absorbed two mols. of hydrogen and gave in good yield a crystalline perhydro-acid; it is assumed to be the *trans*-acid (VI). Decarboxylation gave an 82% yield of a monocarboxylic acid, and a 9% yield of a neutral isomer which was clearly the δ-lactone (VIII). The acid had m. p. −11° to −10°, raised inefficiently to a constant −1·5° on recrystallisation. Evidently part of the acidic product was formed *via* the lactone, and presumably consisted of up to five isomers. This complication lowered the overall yield of the pure geranylacetic acid (VII) and, having obtained poor preliminary results in the reaction with methyl-lithium, we turned our attention to the known geranylacetone semicarbazone; however, the acid may prove useful in other synthetic work.

Despite the precautions taken, geranylacetone, prepared as above and by methods of Dauben and Bradlow [12] for hydrolysis of the keto-ester, gave a semicarbazone with m. p. *ca.* 70°, which was raised to the published value of 96—97° only after about five crystallisations from aqueous ethanol, the best solvent found. The yield, on each recrystallisation, then reached a constant value, and the melting point also remained constant. Treatment with 2 : 4-dinitrophenylhydrazine sulphate gave a derivative which crystallised readily and had m. p. 54—55° (cf. the liquid 2 : 4-dinitrophenylhydrazone obtained by Carroll,[20] and by ourselves from the crude ketone *). We therefore assumed that the semicarbazone was in fact homogeneous. The yield was only 48—62% from the crude ketone, whereas regeneration gave a ketone which was reconverted into a semicarbazone, m. p. 96—97°, after only one crystallisation, in high yield. Again, it is clear that the crude ketone from geranyl chloride, despite the *a priori* reasonable methods used, was far from pure. Since the completion of the present work Stadler *et al.*[21] have reached a similar conclusion regarding " geranylacetone " prepared *via* the bromide, and have described a method of purification by rigorous fractional distillation.

Preliminary attempts to convert the regenerated *trans*-ketone into farnesic acid *via* the ethoxyacetylenic alcohol were discouraging in that the product apparently underwent partial cyclisation on acid-catalysed rearrangement; and neither the crude ethyl farnesate,

* Naves (*Helv. Chim. Acta*, 1949, **32**, 1801) obtained a 2 : 4-dinitrophenylhydrazone, m. p. 72—73°, from a " geranylacetone " obtained by a reverse aldol fission of natural farnesal. This suggests the presence of a *cis*-linkage in the latter.

[17] See, *inter al.*, Winstein and Young, *J. Amer. Chem. Soc.*, 1936, **58**, 104.
[18] Dupont and Labaune, *Wiss. und Industrie Ber.*, Rour-Bertrand Fils, 1911, (III), **3**, 3; *Chem. Zentralblatt*, 1911 (II), **15**, 138.
[19] Forster and Cardwell, *J.*, 1913, 1338.
[20] Carroll, *J.*, 1940, 704.
[21] Stadler, Nechvatal, Frey, and Eschenmoser, *Helv. Chim. Acta*, 1957, **40**, 1373.

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nor the derived farnesol, formed a thiourea clathrate. Attention was turned to the possible use of the Wittig reagent from 1 : 4-dibromobutane to give squalene directly. Triphenylphosphine and the dihalide gave a good yield of the 4-bromobutyltriphenylphosphonium bromide in boiling butan-2-one, and this reacted with another molecule of triphenylphosphine in boiling *cyclo*hexanone, giving a salt of which the dihydrate, m. p. 146—149°, was converted with some difficulty into an anhydrous product, m. p. 300—308°. Addition of ethereal butyl-lithium solution to an excess of the salt gave only a transient yellow coloration; but when the salt was added gradually to the butyl-lithium solution (in tetrahydrofuran) it dissolved almost completely, and a deep red solution of the Wittig reagent resulted. Addition of the ketone decolorised the solution with the formation of a precipitate, which was decomposed under nitrogen at 60°. Extraction with light petroleum and chromatographic purification gave a hydrocarbon (15% yield) of which the infrared spectrum was identical with squalene.

Trippett's brief description [13] of the reaction between geranylacetone and 1 : 4-dibromobutane appeared when the Wittig reaction was under investigation in these laboratories, and his use of tetrahydrofuran as solvent prompted us to employ it.

The hydrocarbon obtained gave a crystalline precipitate when treated with thiourea in methanol–benzene, from which the regenerated all-*trans* hydrocarbon was obtained in 6—13% yield. Treatment of the mother-liquors with further quantities of thiourea failed to produce more clathrate; on the other hand the once regenerated hydrocarbon gave the same yield (75—80%) in a further purification cycle as did once regenerated natural squalene in duplicate small-scale experiments. Infrared spectra of the regenerated synthetic and the natural substance are illustrated, together with that of the hydrocarbon which refused to form a clathrate. Such spectra are evidently unsuitable for distinguishing between stereoisomers of the polyisoprene type, although they would reveal the presence of even a small proportion of any prototropic isomer with a $>C=CH_2$ grouping.

Dr. N. Nicolaides and Dr. F. Laves have examined the clathrate of synthetic squalene, and report that the length of the hydrocarbon chain is the same, within experimental error of $\pm 0{\cdot}1$ Å, as that of natural squalene. He was, however, able to prepare, from a sample of the hydrocarbon which we had tried to free from the all-*trans*-form by treatment with thiourea, a certain amount of thiourea clathrate which showed an inclusion chain-length measurably shorter than that of the *cis*-hydrocarbon. This would correspond to the presence of one or more *cis*-linkages,[6] with some distortion of the molecule from its most stable conformation which is apparently unsuited to clathrate formation.

Although we believe that, in the combination of infrared scrutiny and the formation and *X*-ray examination of clathrates, definitive physical methods for the comparison of stereoisomeric unconjugated polyenes are at last available, it remained necessary, for complete satisfaction, to prove the identity of the natural and synthetic hydrocarbons toward an enzymic system. Dr. K. Bloch, Dr. T. T. Tchen, and Dr. R. K. Maudgal have now obtained conclusive evidence on this point, which will be described in detail elsewhere.

## Experimental

*trans*-4 : 8-*Dimethylnona*-3 : 7-*diene*-1 : 1-*dicarboxylic* ("*Geranylmalonic*") *Acid*.—Geraniol (25 g.; regenerated from its calcium chloride complex), dry pyridine (13·8 g.), and dried ether (100 c.c.) were stirred at $-20°$ to $-10°$ while thionyl chloride (22·3 g.; redistilled over quinoline, then linseed oil) was added during 1 hr. Dry ether (100 c.c.) was added, and the solution was stirred overnight at room temperature. The supernatant liquid was decanted from the pyridine hydrochloride, which was washed with ether (2 × 50 c.c.), and the ethereal solution was washed successively with much water, sodium hydrogen carbonate solution to neutrality, dilute sulphuric acid until no more pyridine was removed, sodium hydrogen carbonate solution, and water, and dried ($Na_2SO_4$). Evaporation at 10 mm. gave a liquid (25·0 g.) which showed bands at 835, 895, 925, 990 cm.$^{-1}$ attributable respectively to $>C=CH-$, unconjugated vinyl, conjugated vinyl, and unconjugated vinyl groupings. This was added dropwise to a solution of

the sodium derivative of ethyl malonate, prepared from sodium (6·7 g.) and the ester (57·6 g.) in dry ethanol (200 c.c.). The mixture was heated under reflux during 6 hr. with mechanical stirring. Water (400 c.c.) was added and the neutral fraction was isolated with ether. After removal of the solvent, distillation from a Kon flask gave (*a*) ethyl malonate, (*b*) a mixture (of terpene hydrocarbons, geraniol, and $C_{10}$ ethyl ethers), b. p. 90—97°/0·15 mm., and (*c*) the required ester (17·5 g.), b. p. 97—100°/0·15 mm., $n_D^{19}$ 1·4610 (Barnard and Bateman [9] give b. p. 126—129°/0·2 mm., $n_D^{20}$ 1·4610).

This was heated with 10% potassium hydroxide solution (150 c.c.) under reflux for 15 hr., the upper layer disappearing. Isolation of the acidic fraction gave a syrup (12·7 g.), which crystallised partly at −78°. A solution in methylene dichloride (30 c.c.) was held at −78° for 18 hr., and the liquid was removed as completely as possible from the separated solid. After repetition of this process (necessarily inefficient because of the fibrous crystals obtained) from 30 c.c., then from 10 c.c., of methylene dichloride the product (5·0 g.; m. p. 41—45°) was crystallised from light petroleum containing a little ether at 0°, giving 4·0 g. of the essentially pure *acid*, m. p. 46—48°, finally raised to 50·5—51·5° on further crystallisation (Found: C, 64·75; H, 8·25. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·35%). (The overall yield of essentially pure acid from geraniol varied from 11 to 13%.)

4 : 8-*Dimethylnonane*-1 : 1-*dicarboxylic Acid*.—Crystalline geranylmalonic acid (65 mg.) was hydrogenated in glacial acetic acid (10 ml.) in the presence of palladium–calcium carbonate (35 mg.) for 30 min. at 20° [uptake 2·3 mols.]. After filtration and evaporation the product solidified. Crystallisation from pentane at −78° gave the *acid*, m. p. 56—57° (Found: C, 63·85; H, 10·05. $C_{13}H_{24}O_4$ requires C, 63·95; H, 9·85%).

trans-5 : 9-*Dimethyldeca*-4 : 8-*dienoic* (*Geranylacetic*) *Acid*.—Geranylmalonic acid (6·6 g.; m. p. 46—49°) was heated in nitrogen at 0·05 mm.; decomposition began at 145° and was completed by raising the bath-temperature during 1 hr. to 165°. The distillate (4·9 g.) was dissolved in ether and shaken with sodium carbonate solution. The latter was acidified and the acidic fraction was isolated with ether, giving, after removal of solvent at 0·05 mm., the crude acid (4·45 g., 83%), m. p. −11° to −10°, raised economically to −7° on one crystallisation from pentane, or in *ca.* 25% yield after five crystallisations and redistillation to −1·5° [b. p. 115° (bath-temp.)/0·05 mm., $n_D^{22}$ 1·4718]. The S-*benzylisothiuronium salt* formed plates, m. p. 128—129°, from aqueous ethanol (Found: N, 7·40. $C_{19}H_{30}O_2N_2S$ requires N, 7·73%). Distillation of the neutral fraction gave 5-*hydroxy*-5 : 9-*dimethyldec*-8-*enoic lactone* (450 mg.), b. p. 100—120° (bath-temp.)/0·01 mm. (Found: C, 73·0; H, 10·1. $C_{12}H_{20}O_2$ requires C, 73·45; H, 10·2%).

Similar decarboxylation of the syrup from the geranylmalonic acid mother-liquors (7·16 g.) gave a monocarboxylic fraction (3·6 g., 61%) which failed to solidify even at −78° or on treatment with light petroleum at low temperatures and seeding. Its *S*-benzyl*iso*thiuronium salt had m. p. 119—125° initially, raised to 124—131° after four crystallisations, but still evidently heterogeneous.

trans-6 : 10-*Dimethylundeca*-5 : 9-*dien*-2-*one* ("*Geranylacetone*").—The crude geranyl chloride (211 g.) obtained from geraniol (200 g.) was added to a solution prepared from sodium (36·8 g.) and ethyl acetoacetate (273 g.) in dried ethanol (750 c.c.), and the mixture was heated under reflux with mechanical stirring for 6 hr. Water (3 l.) was added, and the neutral fraction was isolated with ether. After removal of the solvent at 10 mm., the residue (279 g.) was added to a solution of sodium hydroxide (70 g.) in water (2 l.) and ethanol (3 l.). The mixture was heated under reflux for 48 hr., water (5 l.) was added, and the neutral fraction was isolated with ether. Addition of benzene and removal of solvents at 10 mm., followed by distillation from a Kon flask, gave a series of fractions (45·5 g.), b. p. 53—61°/0·1 mm., $n_D^{18}$ 1·4596—1·4640, which were rejected, followed by others (107·5 g.), b. p. 62—68°, $n_D^{18}$ 1·4655—1·4686, which were added to a solution of semicarbazide hydrochloride (67 g.) and sodium acetate trihydrate (100 g.) in water (650 c.c.) and ethanol (750 c.c.). The solution was warmed at 50° for 30 min. and cooled to 0°; the precipitated semicarbazone was collected, then crystallised five times from 1 : 1 v/v water–ethanol (10 c.c. per g.). The recovery rose gradually from 84% to a constant 94%, the crystals, originally small and indefinite, became large, transparent plates, and the m. p. rose from 85—94° to 96·5—97·5° (yield 66 g.) (Forster and Cardwell [19] give m. p. 97°).

The semicarbazone (66 g.) dissolved when shaken with 2N-sulphuric acid (1·5 l.) and light petroleum (b. p. 40—60°; 1·5 l.) for 24 hr. at ~22°. Evaporation of the solvent and distillation gave the *trans*-ketone (48·2 g., 19% from geraniol), b. p. 60—61°/0·05 mm., $n_D^{22}$ 1·4661, $n_D^{16}$

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1·4688 (Found: C, 80·35; H, 11·2. Calc. for $C_{13}H_{22}O$: C, 80·3; H, 11·4%). It gave a semicarbazone which after *one* crystallisation had m. p. 96—97°. The 2 : 4-*dinitrophenylhydrazone* formed orange plates, m. p. 54—55°, from ethanol (Found: C, 61·2; H, 7·05. $C_{19}H_{26}O_4N_4$ requires C, 60·9; H, 7·0%).

*4-Bromobutyltriphenylphosphonium Bromide.*—Triphenylphosphine (78 g.), 1 : 4-dibromobutane (43 g.), and butan-2-one (300 c.c.) were heated under reflux for 12 hr. After cooling, the *product* (93 g., 98%) was collected, washed with ether, and dried. It formed plates, m. p. 207—212°, from water (Found: C, 55·3; H, 4·7. $C_{22}H_{23}PBr_2$ requires C, 55·25; H, 4·8%).

*Tetramethylene-1 : 4-bistriphenylphosphonium Bromide.*—The above salt (103 g.), triphenylphosphine (173 g.), and *cyclo*hexanone (1600 c.c.) were heated under reflux for 48 hr. On cooling, two layers formed; the lower layer was dissolved in hot water (200 c.c.), the hydrated salt (84 g.), m. p. 146—149° with resolidification, separating on cooling. Further quantities of hydrate separated from the *cyclo*hexanone layer, bringing the total yield to 122 g., *i.e.*, 77% of the dihydrate. Prolonged drying of the finely ground hydrate at 100°/0·05 mm. over phosphoric oxide gave the anhydrous salt, m. p. 300—308°.

*all*-trans-2 : 6 : 10 : 15 : 19 : 23-*Hexamethyltetracosa*-2 : 6 : 10 : 14 : 18 : 22-*hexaene* (*Squalene*). —A solution of butyl-lithium in ether was prepared by the action of *n*-butyl bromide on lithium (6·45 g.) at −10°, and estimated, after filtration through glass wool into a flask filled with nitrogen, by the double-titration method.[23] A portion (45 c.c., containing 0·062 mole) was added to purified tetrahydrofuran (100 c.c.), and the mixture was stirred under nitrogen while the finely powdered dibromide (22·9 g., 0·031 mole) was added during 10 min. The solution became deep red, but some of the salt remained undissolved. *trans*-6 : 10-Dimethylundeca-5 : 9-dien-2-one (12·0 g.) in anhydrous tetrahydrofuran (50 c.c.) was at once added dropwise; a white precipitate was formed, the solution becoming almost colourless. The mixture was heated under reflux for 1 hr., the solvent removed at 10 mm., and the semi-solid residue heated in nitrogen for 5 hr. at 60°. The resultant material was extracted with light petroleum (b. p. 60—80°; 5 × 100 c.c.), the extract was concentrated, and insoluble matter was removed by centrifugation. Evaporation gave an oil (11·2 g.) which was chromatographed on alumina (500 g.; grade " H ") with light petroleum (b. p. 60—80°) as eluant. The hydrocarbon fraction so obtained (1·95 g., 15%) had an infrared spectrum indistinguishable from that of squalene; yields varied from 13 to 22%.

The hydrocarbon mixture in benzene (24 c.c.) was added in one portion to a saturated solution of thiourea in methanol (160 c.c.) with swirling. After 1 hr. at 0° the adduct (1·50 g.) formed fine needles; a further crop (0·97 g.) separated overnight. The first crop was decomposed by shaking it with water (50 c.c.) and light petroleum (b. p. 40—60°; 50 c.c.), and the extract was washed with water, dried ($MgSO_4$), and evaporated, giving the hydrocarbon (122 mg., 6·3%) (in other experiments yields, based on the hydrocarbon mixture, were 10·5—13%) (Found: C, 87·8; H, 12·2. Calc. for $C_{30}H_{50}$: C, 87·7; H, 12·3%).

*Mixture of the* $\Delta^{10}$-cis- *and the* $\Delta^{10:14}$-*Di*-cis-*isomer.*—Recovery of the hydrocarbon by dilution of the methanol–benzene–thiourea solution with water and extraction with light petroleum gave an oil (1·7 g.) which was again treated with benzene (20 c.c.) and thiourea–methanol (135 c.c.), giving a slight precipitate which was removed. Re-isolation and re-chromatography gave a colourless liquid (1·40 g.) with the infrared spectrum illustrated (Found: C, 87·6; H, 12·1%).

Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics.

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, December 17th*, 1957.]

[23] Gilman and Haubein, *J. Amer. Chem. Soc.*, 1944, **66**, 1515.

## 408. *The Relationship between Proton Dissociation Constants and the Stability Constants of Complex Ions.*

By J. G. Jones, J. B. Poole, J. C. Tomkinson, and R. J. P. Williams.

The proton, acid, dissociation constants of some derivatives of salicylaldehyde and of 8-hydroxyquinoline (oxine) have been determined, and compared with the stability constants of the complexes formed by the ligands derived from these acids and several cations. The relationship between these quantities is more complicated than has been assumed hitherto. The discussion is supported by reference to the absorption spectra of the metal complexes. The general approach can be extended to other series of ligands.

Several authors [1,2,3] have suggested that a general linear relation exists between the logarithms of the stability constants, log $K$, of a series of 1 : 1-complex ions, ML, derived from one metal, M, with a set of similar ligands, L, and the logarithm of the acid dissociation constants, p$\kappa$, of the ligands. The general form

$$\log K = a\,\mathrm{p}\kappa + b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $a$ and $b$ are constants, was first used by Bjerrum [3] and much discussed by Martell and Calvin.[2] Specific examples of the relation had been examined earlier.[4,5] Duncan [6] derived a thermodynamic relation:

$$\log K = \mathrm{p}\kappa - [G(^\circ_{\mathrm{ML}} - G^\circ_{\mathrm{HL}})/\boldsymbol{RT}] + B \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $G^\circ_{\mathrm{ML}}$ and $G^\circ_{\mathrm{HL}}$ are the partial molar free energies of the species ML and HL respectively and $B$ is a constant independent of L. This relation has been further discussed by Irving and Rossotti.[7]

From relation (2) the constant $a$ in equation (1) could only be unity if changes of $G^\circ_{\mathrm{ML}}$ and $G^\circ_{\mathrm{HL}}$ with ligand compensated one another exactly. If an equation of the general form of (1), where $a$ is not necessarily unity, is to be derived from (2) then the dependence of $G^\circ_{\mathrm{HL}}$ upon the ligand must be similar to that of $G^\circ_{\mathrm{ML}}$. Such dependences cannot be deduced from thermodynamic arguments (cf. ref. 7) but require a discussion of the bonding in HL and ML. We recognise here that although both $G^\circ_{\mathrm{HL}}$ and $G^\circ_{\mathrm{ML}}$ depend similarly upon one property of the ligand, the $\sigma$-donor (or -acceptor) power, they must differ in their dependence on its $\pi$-donor (or -acceptor) character. Most strong $\sigma$ donor substituents in ligands are also $\pi$ donors, *e.g.*, methyl, and most strong $\sigma$ acceptors are also $\pi$ acceptors, *e.g.*, nitro, so that a change of substituent in a ligand causes changes in $\sigma$- and $\pi$-electron densities which are usually in the same direction.

Cations such as the cupric ion are $\pi$-electron donors [8] so that they should be less destabilised in a complex than the proton by $\sigma$-electron-acceptor substituents which are also $\pi$-electron acceptors, and less stabilised by $\sigma$-electron donors which are also $\pi$-electron donors. Thus the slope $a$ of the plot of log $K$ for cupric complexes against p$\kappa$ should be less than unity on these grounds alone. Conversely $a$ will exceed unity for a cation which is a $\pi$-electron acceptor.

For ligands with substituents not of this general kind (*e.g.*, the chloro-group is a $\pi$ donor but a $\sigma$ acceptor), the linear relation between p$\kappa$ and log $K$ observed for substituents in

[1] Schwarzenbach, Anderegg, Schneider, and Senn, *Helv. Chim. Acta*, 1955, **38**, 1147.
[2] Martell and Calvin, "The Chemistry of The Metal Chelates," Prentice-Hall, New York, 1953, p. 76.
[3] Bjerrum, *Chem. Rev.*, 1950, **46**, 381.
[4] Bruehlman and Verhoek, *J. Amer. Chem. Soc.*, 1948, **70**, 1401.
[5] Britton and Williams, *J.*, 1935, 796.
[6] Duncan, *Analyst*, 1952, **77**, 830, and personal communication.
[7] Irving and Rossotti, *J.*, 1954, 2904, 2910; *Acta Chem. Scand.*, 1956, **10**, 72.
[8] Tichane and Bennett, *J. Amer. Chem. Soc.*, 1957, **79**, 1293.

the general case should no longer be obeyed. The fact that relation (1) holds is somewhat fortuitous and depends upon a particular choice of ligand substituents. Before developing this discussion we will present new evidence that in some series of ligands, and depending on the choice of substituents, relations of the form (1) do not hold and in some others they are far from exact. Equation (1) has no general validity; as this is obvious if ligands of somewhat different character are compared, we shall only compare similar ligands for which the relation has been most intensively examined.

*The Stability of Metal Oxine Complexes.*—In their discussion of the relationship expressed by equation (2) Irving and Rossotti [7] produced evidence which they took to prove linear relationships between the acid dissociation constants of the phenol group of a series of 8-hydroxyquinolines and the stability constants of the individual series of the zinc, nickel, magnesium, uranyl, and cupric complexes. Additional ligands of the same series and their complexes with ferrous and ferric ions have now been examined.[9] As we did not

FIG. 1.

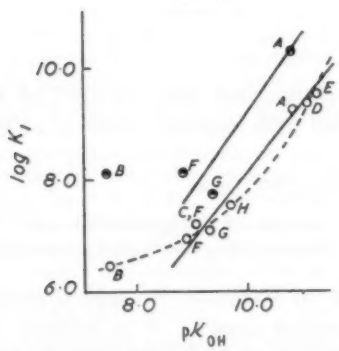


FIG. 2.

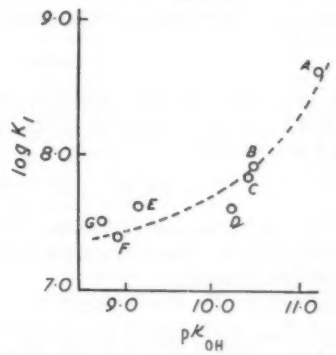


FIG. 1. *The relation between the dissociation constant of the phenolic group of oxines,* $pK_{OH}$, *and the stability constants of the nickel,* ◓, *and zinc,* ⊙, *oxine complexes.* Full lines, Irving and Rossotti; broken line, present work (see Table 1).

*A*, 8-Hydroxyquinoline; *B*, 5-formyl-8-hydroxyquinoline; *C*, 8-hydroxy-4-methylquinoline; *D*, 8-hydroxy-5-methylquinoline; *E*, 8-hydroxy-7-methylquinoline; *F*, 8-hydroxycinnoline; *G*, 8-hydroxyquinazoline; *H*, 8-hydroxyquinoxaline; *C,F*, 8-hydroxy-4-methylcinnoline.

FIG. 2. *The relation between the dissociation constant of the phenolic group of oxines,* $pK_{OH}$, *and the stability constants of the ferrous oxine complexes* (*see Table* 1).

*A*, 8-Hydroxyquinoline; *B*, 5-bromo-8-hydroxy-; *C*, 5-chloro-8-hydroxy-; *D*, 8-hydroxy-5-iodo-; *E*, 5-chloro-8-hydroxy-7-iodo-; *F*, 8-hydroxy-5 : 7-di-iodo-; *G*, 5 : 7-dichloro-8-hydroxy-quinoline.

find a simple relation between $pK$ and log $K$ for these two metals we studied further the complexes of zinc, nickel, and manganous ions with 5-formyl-8-hydroxyquinoline. The conditions used were similar to those of Irving and Rossotti and all calculations of constants are modelled on their methods.[10] Fig. 1 incorporates both sets of results for zinc and nickel ions. Fig. 2 gives data for the ferrous complexes (Table 1). We cannot draw linear plots between $pK_{OH}$ and log $K$ for these or for the other cations studied.

The linear relation between $pK_{OH}$ and log $K$ suggested by Irving and Rossotti (full lines in Fig. 1) for some of the same metals and ligands arose because their study was limited to two *particular groups of ligands*: (1) substituted oxines with dissociation constants very near those of oxine itself, and (2) oxines in which a second ring nitrogen atom has been substituted. When a wider range of substituents is used the relation (1) is no longer obeyed. Moreover substituents in this series of ligands have specifically different effects

[9] Tomkinson and Williams, following paper.
[10] Irving and Rossotti, *J.*, 1953, 3397.

on one metal from those on another, *e.g.*, in ferrous and ferric complexes.[9] Lastly, from eqn. (1) a linear relation might be expected between pκ and the oxidation–reduction potentials of the ferrous–ferric couples, but this is not found.[9]

TABLE 1. *Stability constants of oxine complexes.*

*A.* 5-Formyl-8-hydroxyquinoline complexes in 50% dioxan–water (v/v) ($p\kappa_{OH}$ = 7·43).

| | $Ni^{II}$ | $Fe^{II}$ | $Zn^{II}$ | $Mn^{II}$ | $Fe^{III}$ |
|---|---|---|---|---|---|
| log $K_1$ | 8·27 | 6·90 | 6·45 | 5·73 | 11·7 |
| log $K_2$ | 7·56 | 6·85 | 6·25 | 4·97 | 10·0 |
| log $K_3$ | 6·70 | 5·70 | 4·95 | 4·58 | 8·3 |

*B.* Ferrous 8-hydroxyquinoline complexes in 75% dioxan–water (v/v).

| Subst. | None | 5-Cl | 5-Br | 5-I | 5 : 7-$Cl_2$ | 5-Cl, 7-I | 5 : 7-$I_2$ |
|---|---|---|---|---|---|---|---|
| $p\kappa_{OH}$ | 11·22 | 10·47 | 10·45 | 10·27 | 8·83 | 9·07 | 8·96 |
| $p\kappa_{NH}$ | 3·14 | 1·94 | 1·93 | 1·64 | ~0·9 | ~1·5 | ~0·5 |
| log $K_1$ | 8·58 | 7·86 | 7·92 | 7·58 | 7·50 | 7·61 | 7·40 |
| log $K_2$ | 8·35 | 8·07 | 8·19 | 8·13 | 7·31 | 7·80 | 7·69 |
| log $K_3$ | 5·30 | 4·50 | 5·30 | 5·35 | 4·50 | 4·84 | 4·25 |

The pκ values are practical dissociation constants; for these and other values used in Fig. 1, see ref. 7.

Alternatively, by plotting log $K$ against the sum of the pκ values for the two acidic centres in oxines ($p\kappa_{OH} + p\kappa_{NH}$) we find a somewhat more satisfactory agreement with eqn. (1), but the value of $a$ for the cupric complexes is now 0·7 instead of 2·2. Whichever

FIG. 3. *The relation between the dissociation constants of salicylaldehydes and the stability constants of the cupric salicylaldehyde complexes,* ○, *as compared with the same data for 2-hydroxy-1-naphthaldehyde,* ●, *and for a series of acetylacetone complexes,* ◓ (*see Table* 2).

*A*, Acetylacetone; *B*-trifluoroacetylacetone; *C*, hexafluoroacetylacetone; *D*, salicylaldehyde; *E*, 3-methyl-; *F*, 4-chloro-; *G*, 3-methoxy-; *H*, 5-chloro-; *I*, 5-bromo-; *J*, 3-chloro-; *K*, 3-nitro-; *L*, 5-nitro-; *M*, 3 : 5-dinitro-salicylaldehyde (CHO = 1).

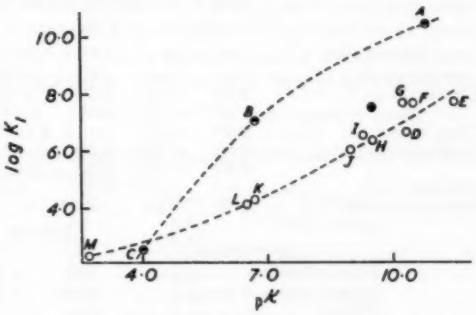


TABLE 2. *Acid dissociation constants and stability constants of cupric complexes of salicylaldehyde derivatives.*

| In 50% Dioxan–Water | | | | In 75% Dioxan–Water | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Substituent | pκ | log $K_1$ | log $K_2$ | Substituent | pκ | log $K_1$ | log $K_2$ | Substituent | pκ | log $K_1$ | log $K_2$ |
| None ..... | 9·50 | 7·05 | 5·63 | None ..... | 10·35 | 6·70 | 6·00 | 5-bromo ... | 9·25 | 6·35 | 5·65 |
| 5-methyl ... | 9·70 | 7·15 | 5·71 | 3-methyl ... | 11·50 | 7·50 | 6·70? | 5-nitro ..... | 6·55 | 4·10 | 3·50 |
| 5-methoxy | 9·65 | 6·76 | 5·60 | 3-methoxy | 10·20 | 7·50 | 6·40 | 3-nitro ..... | 6·70 | 4·20 | 3·40 |
| 3-methoxy | 9·10 | 7·17 | 5·45 | 3-chloro ... | 8·70 | 5·86 | 4·90 | 3 : 5-dinitro | 2·60 | 2·20 | 1·40? |
| 5-nitro ..... | 5·85 | 4·16 | 3·60? | 4-chloro ... | 10·50 | 7·50 | 6·50 | (2-hydroxy-1- | | | |
| (Acetyl- | | | | 5-chloro ... | 9·35 | 6·10 | 5·30 | naphthalde- | | | |
| acetone | 9·70 | 9·40 | 8·03) | | | | | hyde ..... | 9·35 | 7·35 | 6·52) |

The acid dissociation constants are practical constants. Values marked (?) are uncertain to ±0·20; others are uncertain to ±0·10. Agreement with Calvin and Wilson's data is satisfactory, differences in conditions of measurement being considered. Values for acetylacetone complexes in Fig. 3 are log $K_1$—2·0 from ref. 12, and not from this Table.

method is adopted of plotting the results, no exact linear relationship is obtained for any cations; the same conclusion can be reached from other data.[11]

*Stability of Metal Salicylaldehyde Complexes.*—Restudying the interaction between derivatives of salicylaldehyde and cupric ions, we obtained the results in Fig. 3. By a

[11] Albert and Hampton, *J.*, 1954, 505.

suitable choice of substituent $p\kappa$ and log $K$ cover a very considerable range. Although the linearity expressed by eqn. (1) with $a = 0{\cdot}68$ is obeyed to a good approximation, several marked deviations are found. For example, 4-chloro- and 3-methoxy-salicylaldehyde cupric complexes are abnormally stable relative to the $p\kappa$ values for these ligands. The general scatter of points about the best straight line will be shown to be significant. In Fig. 3 a curve has been drawn through the points in order to contrast the data with those for the acetylacetone complexes.[12]

Calvin and Wilson [13] found, but did not comment on, the fact that although there was a rough linear relation between $p\kappa$ and log $K$ many salicylaldehyde derivatives also gave results deviating strongly from it. For example, the 4-nitro- and 4 methoxy-salicylaldehyde complexes did not behave as expected. Somewhat larger deviations were observed for naphthaldehyde complexes but these were explained by a treatment discussed below. These authors suggested that different series of complexes of aromatic aldehydes, salicylaldehydes, and naphthaldehydes, and a series of complexes of acetylacetone gave rise to relations of type (1) where $a$ is approximately the same for all the series but $b$ changes from series to series. Their best straight lines were of slope $a = 0{\cdot}70$. Now the value of $a$ in this series of ligands is so different from that found [7] in the cupric oxine complexes, $a = 2{\cdot}2$, despite the fact that the dissociation constant of a phenolic group is used as a measure of basicity in both cases, that we decided to examine other series of ligands in order to find how $a$ and $b$ varied with ligand series.

TABLE 3. *Values of the constants in eqn.* (1).

| | Zinc | | Cupric | | Nickel | | Magnesium | | Note * |
|---|---|---|---|---|---|---|---|---|---|
| Ligand class | $a$ | $b$ | $a$ | $b$ | $a$ | $b$ | $a$ | $b$ | |
| Acetylacetone † ..... | — | — | 0·70 | +3·8 | 0·55 | +3·2 | — | — | (1) |
| Oxine ($p\kappa_{OH}$) † ..... | 1·10 | −3·0 | 2·20 | −11·0 | 1·40 | −4·5 | 1·00 | −6·0 | see p. 2003 |
| ,, ($p\kappa_{OH} + p\kappa_{NH}$) ... | 0·50 | +2·0 | 0·75 | +1·5 | 0·45 | +3·5 | 0·40 | −1·0 | see p. 2003 |
| Tropolone † ..... | 0·70 | +1·1 | — | — | 0·72 | +0·6 | 0·44 | +1·8 | (2) |
| Imidodiacetic acid ..... | 0·90 | −3·3 | 1·03 | −1·0 | 1·04 | −3·8 | 0·50 | −2·3 | (5) |
| | 0·85 | −3·5 | 1·33 | −5·0 | 1·10 | −4·5 | — | — | |
| Phthalic acid ..... | — | — | 0·75 | −0·8 | 0·50 | −0·5 | — | — | (3) |
| Phenanthroline ..... | 0·40 | +4·0 | — | — | — | — | — | — | (4) |

| | Ferrous | | Ferric | | |
|---|---|---|---|---|---|
| Ligand class | $a$ | $b$ | $a$ | $b$ | Note |
| Phenanthroline ..... | 0·85 | +3·0 | 1·50 | −1·0 | (4) |
| Oxine † ($p\kappa_{NH} + p\kappa_{OH}$) ..... | 0·50 | +3·0 | 0·90 | +5·0 | see p. 2003 |
| Phenol ..... | — | — | 0·97 | −1·0 | |

* See text.

The constants refer to best straight lines drawn through series of points which are often some distance from the lines. The values of $a$ and $b$ are liable to errors of $\pm 0{\cdot}1$ and $\pm 1{\cdot}0$ respectively. Series marked (†) refer to measurements in 50% dioxan–water and unmarked series refer to measurements in water. Change of solvent alters $a$ only slightly but has a considerable effect upon $b$, although even the latter effect is probably within the " error " of the best straight lines.

Table 3 includes all the relevant data. Many of the complexes involve co-ordination through enolic or phenolic oxygen atoms. In most of the ligand series the ligand binds the cation through at least one other centre. The basicity of the second co-ordinating group is not always known, as for example in salicylaldehyde, so that in plotting the dissociation constant $p\kappa$ of one of the groups against log $K$, it is not to be expected that an exact relation, if any, will be found. As we have seen for 8-hydroxyquinolines, use of only one acidic dissociation constant ($p\kappa_{OH}$) causes the linear relation (1) to break down. Several other relevant comments are now given as notes to Table 3

*Notes to Table* 3.—1. There is a number of exceptional ligands amongst the acetyl acetones and Van Uitert, Fernelius, and Douglas [12] prefer to draw a non-linear relation between $p\kappa$ and log $K$ at low $p\kappa$ values (see Fig. 3). Van Uitert *et al.* also point out that the

[12] Van Uitert, Fernelius, and Douglas, *J. Amer. Chem. Soc.*, 1953, **75**, 457; Van Uitert and Fernelius. *ibid.*, p. 3862.
[13] Calvin and Wilson, *ibid.*, 1945, **67**, 2003.

values of *a* are almost independent of the type of substituent. They give slightly different values to the constant *b* for the series of ligands which have aromatic and aliphatic substituents in acetylacetone respectively.

2. The α- and β-substituted tropolones [14] do not give rise to the same relation; *b* differs although *a* may be the same.

3. 3-Substituted phthalic acids behave exceptionally.[15] Such substituents appear to stabilise the cupric complexes more than expected from the magnitude of pκ. This has also been observed amongst salicylaldehydes.[13]

4. Only a few complexes with different substituents have been studied.[16] The redox potential of the $Fe^{II}$–$Fe^{III}$ couple has been studied for a more extensive series of substituents. Now the value of the redox potential should be linear with pκ if eqn. (1) holds for both ferrous and ferric complexes, but this is not so.[9] The dipyridyls give a different relation from the phenanthrolines.

5. A re-plot of the data for the imidodiacetates [8] does not give a good linear relation so that values of *a* and *b* quoted may be in considerable error. There is some disagreement between the two sets of data.[1,8]

The surprising fact revealed by Table 3 and its notes is that, although a rough linear relation is found between log *K* and pκ for certain types of simple substituent, *e.g.*, for methyl, chloro-, and nitro-groups in salicylaldehyde, most authors stress that the relation fails if the conjugated system of the ligand extends through carbon chains, *e.g.*, a phenyl substituent in acetylacetone, a change from salicylaldehyde to naphthaldehyde, or the change from dipyridyl to *o*-phenanthroline amongst imines. Now it is usually supposed that a substituent such as a nitro-group interacts with a conjugated hydrocarbon in much the same way as an extension of the conjugation: there should thus be changes in both σ- and π-electron densities throughout the molecule. Such changes might well alter the

TABLE 4.

Relative stabilities of complexes of cupric ion with salicylaldehydes substituted *ortho*, *meta*, and *para* to the hydroxyl groups (*i.e.*, at positions 3, 4, and 5 respectively).

| Substituent | | *ortho* | *meta* | *para* | Solvent |
|---|---|---|---|---|---|
| Nitro | pκ | 6·0 | 7·4 | 5·9 | 50% dioxan |
| | log $K_1$ | 4·15 | 4·9 | 4·35 | |
| Methoxy | pκ | 9·10 | 9·3 | 9·65 | 50% dioxan |
| | log $K_1$ | 7·17 | 7·5 | 6·76 | |
| Chloro | pκ | 8·70 | 10·50 | 9·35 | 75% dioxan |
| | log $K_1$ | 5·86 | 7·50 | 6·10 | |

Relative stabilities of complexes of zinc and nickel ions with 8-hydroxyquinolines having aza-substituents *ortho*, *meta*, and *para* to the nitrogen group (*i.e.*, 8-hydroxy-cinnoline, -quinazoline, and -quinoxaline respectively).

| | *ortho* | *meta* | *para* |
|---|---|---|---|
| ($pK_{NH}$ + $pK_{OH}$) | 10·61 | 12·89 | 10·30 |
| log $K_1$ (Zinc) | 6·93 | 7·48 | 7·07 |
| log $K_1$ (Nickel) | 9·48 | 10·56 | 9·66 |

The relative order of stabilities *para* > *ortho* for π-electron acceptors differs from that, *ortho* > *para*, for π-electron donors. *meta*-Substituted complexes are more stable when the substituent is a π-electron donor.

stability of HL in a manner different from that of ML. In order to exaggerate such differences it is preferable to examine a group of ligands in which the same single substituent is placed in the *ortho*-, *meta*-, and *para*-positions to the acidic centre in turn rather than merely to vary the substituent in one of these positions. The effects of such changes in the position of one substituent are known in salicylaldehydes and 8-hydroxyquinolines (Table 4). The expected relation between pκ and log *K* is no longer observed. Now if we restrict our examination of the relation (1) to the 4- and 5-substituted salicylaldehydes,

[14] Bryant, Fernelius, and Douglas, *J. Amer. Chem. Soc.*, 1953, **75**, 3784; Bryant and Fernelius, *ibid.*, 1954, **76**, 1696.
[15] Yasuda, Suzuki, and Yamasaki, *J. Phys. Chem.*, 1956, **60**, 1649.
[16] Brandt and Gullstrom, *J. Amer. Chem. Soc.*, 1952, **74**, 3532.

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we find that the 4-substituents give rise to a relation in which *a* and *b* differ from those giving the best straight line through the points for 5-substituents. (The 3-substituents are exceptional in another manner, see footnote.) One explanation of the two relationships is immediately apparent. The cupric ion gains in stability relative to the hydrogen ion if the substituent is a π-electron acceptor, *e.g.*, a 5-nitro-group, as the cupric ion can act as a $d_\epsilon$-electron donor. On the other hand a 5-chloro-group, a π-electron donor, makes the copper complex less stable than the hydrogen complex. The 4-substituents affect the electron density on the phenol oxygen atom much less than the 5-substituents so that the π-electron changes with 5-substituents are greater than with 4-substituents. Hence there are two relations, one referring to *para*-substituents (to the hydroxyl group) having the smaller slope, *a*. The curvature of the line in Fig. 3 can thus be explained. The absorption spectra of the cupric complexes also provide evidence that the π-electron interaction in the metal complexes does occur in the manner described. Extension of conjugation, *e.g.*, in going from dipyridyl to *o*-phenanthroline, will lower the π-electron density on nitrogen or oxygen atoms but will have little effect upon σ-electron density.

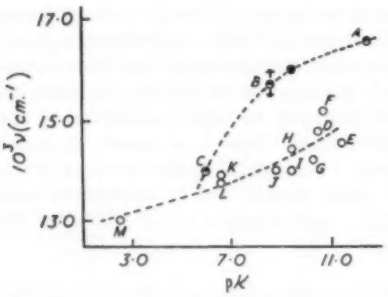


FIG. 4. *The relation between the acid dissociation constants of a series of salicylaldehydes and the frequency of the maximum in the absorption spectra of the cupric salicylaldehyde complexes* ○.

Corresponding data are given for 2-hydroxy-1-naphthaldehyde, ●, and for a series of acetylacetones, ◓.

*A*, Acetylacetone; *B*-trifluoroacetylacetone; *C*, hexafluoroacetylacetone; *D*, salicylaldehyde; *E*, 3-methyl-; *F*, 4-chloro-; *G*, 3-methoxy-; *H*, 5-chloro-; *I*, 5-bromo-; *J*, 3-chloro-; *K*, 3-nitro-; *L*, 5-nitro-; *M*, 3 : 5-dinitro-salicylaldehyde (CHO = 1).

This is why the *o*-phenanthroline complexes are more stable than those of dipyridyl, two ligands of very similar basicity.

*Absorption Spectra of Cupric Complexes.*—We use the theory of the visible absorption spectrum of cupric ion given elsewhere.[17] The ground state is stabilised relative to the excited state either by increase of σ-donor or π-acceptor properties of the ligands. We assume that the σ-properties of the ligand are related to the pκ values so that the lower the pκ the lower the frequency of the absorption maximum. If no other effect had to be taken into account a linear relation might be expected between these quantities.

Fig. 4 shows that relative to those of salicylaldehyde, acetylacetone and naphthaldehyde complexes have absorption spectra at shorter wavelengths than expected on the basis of their respective pκ values. This implies that these ligands act as better $d_\epsilon$ electron acceptors from the cupric ion, as mentioned above. This stabilisation is due to electron migration in the opposite direction to that proposed by Calvin and Wilson,[13] who concluded that the π electrons of the ligand were stabilised by the cation. 3- or 5-Substituents * which are π-electron donors shift the absorption band to lower frequencies and longer wavelengths, and π-electron acceptors shift the band to higher frequencies, than expected on the basis of pκ values. As an example we can compare the cupric complexes of 5-nitro- and 5-bromo-salicylaldehyde. The bromo-group, a π-electron donor, destabilises the ground state but the nitro-group stabilises it relative to the respective pκ values. The absorption maxima of the two complexes are at very similar wavelengths, as expected.

* Some of the 3-substituted salicylaldehydes form complexes with cupric ion which are considerably more stable than the corresponding 5-substituted complexes, *e.g.*, 3-methoxy. The absorption spectra and step stability constants of these complexes are anomalous when compared with 4- and 5-substituted ligand complexes.[14]

[17] Williams, *J.*, 1956, 8.

Other features of Fig. 4 will be discussed elsewhere. Further evidence can be drawn from the study of the fluoro-derivatives of acetylacetone.[18] In Fig. 4 the plot for cupric acetylacetone derivatives shows that for a given change of $p\kappa$ the position of the absorption maximum changes more rapidly than in the salicylaldehyde complexes. The stability of the acetylacetone complexes also changes more rapidly with $p\kappa$ (Fig. 3). The difference between the two series of ligand complexes is attributable to the $\pi$-donor character of the fluoro-substituents in the acetylacetone derivatives as compared with the $\pi$-acceptor character of the nitro-groups in the salicylaldehyde complexes.

We now return to the 8-hydroxyquinoline series. The different correlation between $p\kappa$ and log $K$ obtained by Irving and Rossotti,[7] and by ourselves arose partly from choice of the substituent and partly from the use of only $p\kappa_{OH}$ (instead of $p\kappa_{NH} + p\kappa_{OH}$) as a measure of basic strength. Using either method of examining the data, however, we find that the 5-formyl-8-hydroxyquinoline complexes are more stable than expected from the $p\kappa$ value of the ligand. This we now suggest is due to the strong $\pi$-electron acceptor character of this substituent. A convincing illustration of the influence of such $\pi$-electron acceptor properties in this series is provided by a comparison of the effects of aza-substituents (Table 4); such substituents "*meta*" to the nitrogen group are less effective than those "*ortho*" or "*para*" in stabilising the metal complexes relative to its basicity ($p\kappa_{NH} + p\kappa_{OH}$) in any one of the series of complexes of ferrous,[11] cupric, or zinc[7] ion. This is to be expected as an aza-substituent acts as a $\pi$-electron acceptor but it can only be effective when *ortho* or *para* to the co-ordination position. The position of the absorption band in the ferrous complexes[19,20] confirms that an aza-substituent so placed acts as a strong $\pi$-electron acceptor. The parallel with the discussion of the three mononitrosalicylaldehyde cupric complexes is obvious.

Amongst ferric oxine complexes, those of 5-formyl- and 5-cyano-8-hydroxyquinoline are rather less stable than expected on the basis of $p\kappa$ values. The ferric ion acts as a $\pi$-electron acceptor, unlike the other cations discussed here. It is in part this difference between the ferric ion and the ferrous ion that causes the plot of redox potential against basicity to take such a singular form.[9,20] Albert and Hampton's[11] data show similar differences between ferrous and ferric aza-substituted oxine complexes, although the authors did not comment upon these peculiarities. Lastly, amongst *para*-substituents in ferric phenoxides bromo and methyl stabilise but nitro destabilises the ferric complex relative to the respective $p\kappa$ values of the ligands as in the oxine complexes.[21] In each of these series the absorption spectra of ferric complexes support the conclusion that substituents have opposed effects upon the stability of the ferric and ferrous ground states.[19]

Now all the cations considered above are derived from transition elements which can act as *d*-electron donors or acceptors. The magnesium ion should behave differently. It is not noticeably more stable in cinnoline than in quinazoline complexes,[7] implying that the $\pi$-electron density has little importance in the stability of magnesium complexes.

*Change of* a *with Cation.*—We now discuss eqn. (1) more generally, and assume that deviations from the relation can be understood in such terms as those discussed. For aromatic ligands and $d_\epsilon$-electron donor cations the slope $a$ tends to a value lower than unity owing to the compensating effect of $\pi$ interactions. As expected, the value of $a$ is closer to unity for aliphatic ligands, when there are no $\pi$ effects, for series of cupric, nickel, or zinc complexes, *e.g.*, imidodiacetates (Table 3). We also consider the effect on the slope of a change of cation.

In a simple electrostatic model, with charge $e_1$ on the ligand and charge $e_2$ on the cation, the energy of interaction is $e_1e_2/d$ where $d$, the distance of separation, can be put equal to the radius of the cation plus a constant, $r + c$. If a change in substituent changes $e_1$

[18] Belford, Martell, and Calvin, *J. Inorg. Nuclear Chem.*, 1956, **2**, 11.
[19] Williams, *J.*, 1955, 137.
[20] Williams, *Chem. Rev.*, 1956, **56**, 299.
[21] Milburn, *J. Amer. Chem. Soc.*, 1954, **77**, 2064.

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only, then there will be a linear relationship between pκ and log $K$. The slope will not be unity, but will depend on the differential of $e_1e_2/d$ with respect to $e_1$, *i.e.*, $e_2/d$, and will increase with increasing cationic charge and decreasing $d$. This is found to be so. For example, for lanthanum ($e_2 = 3$) the slope is greater than for barium ($e_2 = 2$) in a series of acetylacetone complexes.[12]

A somewhat more obscure relationship is observed for ions of the same charge but of different size. Our model suggests that the bigger the cation, *i.e.*, the bigger $r$, the smaller the value of $a$. In the cases of the barium acetylacetone and calcium iminodiacetate complexes, $a$ is smaller than for the complexes of the larger cupric ion. In the series of cations $Cu^{II}$, $Ni^{II}$, $Co^{II}$, $Mn^{II}$ the magnitude of the slope $a$ falls in that order, *i.e.*, the stability order found by Irving and Williams. However there is little difference in the size of the cations in this series as compared with the changes in $a$. (This series of $a$ values implies that there cannot be a general relation of unit slope between log $K_{ML}$ for one metal and log $K_{M'L}$ for another, where M and M′ are both in this series of cations.[7]) The order is also the order of the electronegativity of the cations. This parallel was pointed out by Schwarzenbach *et al.*;[1] it implies that $a$ is proportional to the polarisation of the ligand by the cation. Such polarisation can only be expressed in terms of a detailed treatment of the molecular orbitals in transition-metal complexes and here we shall not concern ourselves further with the problem.

*The Values of* b *in Equation* (1).—We make the same assumption as in the discussion of $a$. A comparison of eqns. (1) and (2) shows that $b$ is a composite constant. It comprises the difference in partial molar free energy of the cation and proton, $B$ (independent of the ligand), and terms which are dependent on the ligand, as is shown by eliminating log $K$ between the two equations whereupon we obtain

$$(G^\circ_{ML} - G^\circ_{HL})/RT = (1 - a)p\kappa - (b - B) \quad . \quad . \quad . \quad . \quad . \quad (3)$$

For two ligand series which give rise to the same constant $a$ the term $(b - B)$ will measure the additional stabilisation of one series of ligands, *e.g.*, salicylaldehydes, as compared with another, *e.g.*, acetylacetone, and is assumed here to be independent of the substituents within each series. (We have already shown that this is not exactly true when 4-substituted are compared with 3- or 5-substituted salicylaldehydes but the order of the effect is smaller than the one we are about to discuss.) Table 3 shows that $b$ [or $(b - B)$] changes considerably from aliphatic to aromatic ligands in the order imidodiacetic acid $\leqslant$ phthalic acid $<$ salicylaldehyde (Fig. 3) $<$ naphthaldehyde $<$ acetylacetone $\leqslant$ oxine.

Calvin and Wilson explained a part of this order of $b$, namely salicylaldehyde $<$ naphthaldehyde $<$ acetylacetone, on the basis of resonance between the cation and the ligands. This resonance entailed the transfer of charge from the ligand to the cation. We do not accept this interpretation but believe that the transfer of charge which *in part* controls $(b - B)$ is the transfer of $d_\epsilon$ electrons of the cation, *e.g.*, cupric, to the ligand. The ligand series for which $(b - B)$ is greatest, oxine or acetylacetone, is also the series for which the cupric absorption band is at the shortest wavelength for a given pκ. Following our argument concerning spectra the ligand order given above appears to be dominated by the order of the ability of the ligands to accept electrons through $\pi$ bonding.

It must not be assumed that the only factor affecting $(b - B)$ is $\pi$-bonding. There may well be differences in solvation between ML and HL which are independent of the dissociation constant within a given series but are sensitive to changes from one series of ligands to another. For example, we consider that solvation differences contribute to the difference in relative position between the acetylacetone and naphthaldehyde series in Figs. 3 and 4. Such solvation factors will be of some importance even within a given series, so that a strict linear relation between pκ and log $K$ cannot be expected. Solvation effects should be more or less independent of the cation, especially for cations

of similar charge, whereas the changes in $(b - B)$ due to $\pi$ bonding should depend on the cation. A case in point is the effect of aromatic substituents in acetylacetone complexes upon the $p\kappa$–log $K$ relations.[13] Such substituents have the same effect in barium, cerium, nickel, or cupric complexes and we suspect that the factor common to these different series of cation complexes is one of solvation rather than of $\pi$ bonding.

This paper has been restricted largely to a discussion of relation (1) for bivalent cations. The relation is less applicable to univalent and null-valent cations where $\pi$-bonding is more important. For univalent cations this was shown by Basolo and Murman.[22] Studying the case of the combination of ligands with a cation on which the charge has been neutralised by complex formation with anions we found that there is no relation of the form of eqn. (1).[23] This in turn is due to the increasing importance of $\pi$-effects as the valency of the cation is reduced.

## Experimental

*Materials.*—8-Hydroxyquinoline derivatives were gifts. The salicylaldehydes were prepared by conventional methods. Additional details will be given later of the cupric salicylaldehyde complexes.[24] "AnalaR" metal salts were used to determine stability constants.

*Methods.*—These are well established.[7,8] pH Titrations were used to determine the acid dissociation constants and stability constants of metal complexes. In all cases water–dioxan was used as solvent. The ionic strength in the solutions was constant at 0·3M by addition of sodium perchlorate (cupric experiments) or sodium chloride (other cation experiments). Sodium hydroxide was carbonate free.

The absorption spectra of the complexes were measured on a Unicam S.P. 600 spectrophotometer with matched cells. For the cupric salicylaldehyde complexes the measurements were made in 75% dioxan–water, *i.e.*, the same medium as that in which the stability constants were determined, when this was practicable. All measurements were made at a sufficiently high pH to ensure that the degree of complex formation was $\bar{n} = 2{\cdot}0$. In several cases the spectra were also measured in 50% dioxan–water. No differences were observed in the position of the absorption spectra between the two solvent media. The 5-chloro- and 3 : 5-dinitrosalicylaldehyde cupric complexes were too insoluble in either solvent to permit the determination of their absorption spectra. These spectra were measured in 50% methanol–dioxan by adding a ten-fold excess of ligand in dioxan to cupric chloride in methanol and then raising the pH by adding enough concentrated potassium hydroxide in methanol to neutralise 75% of the ligand. In order that these spectra could be referred to the parent salicylaldehyde complex the same measurements were made with the latter. There was a shift of some 35 mμ to shorter wavelengths from the aqueous solvent to the methanol solvent, and this was allowed for. We did not attempt to analyse the spectra further for, although there are three overlapping *d*–*d* transitions of the cupric ion in the visible region of the spectrum, only one maximum was observed in any measurement. The positions of the maxima in the acetylacetone complexes were taken as 620 mμ for acetylacetone, 625—675 mμ for trifluoroacetylacetone, and 710 mμ for hexafluoroacetylacetone. The first value is that observed in 75% dioxan–water and differs very slightly from the mean of the two peak maxima in chloroform (606 mμ).[18] The other values are those observed in chloroform.[18]

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[22] Basolo and Murman, *J. Amer. Chem. Soc.*, 1955, **77**, 3484.
[23] Jillot and Williams, *J.*, 1958, 462.
[24] Jones, Poole, and Williams, to be published.

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## 409. *Oxidation–Reduction Potentials of Complex Ions.*

By J. C. Tomkinson and R. J. P. Williams.

A new procedure for the study of the oxidation–reduction potentials of complex ions is described, in which the mid-point potential is followed as the pH is varied continuously. The relation between the potentials and the degrees of formation of the complexes is discussed. A series of ferric–ferrous oxine (8-hydroxyquinoline) complex couples was examined. The relative stabilities of the two valency states depend on the electronic states of the respective cations, which are influenced by the ligand field.

The factors controlling the oxidation–reduction potentials of complex ions have never been systematically studied for a sufficiently wide range of complexes to yield any general theory. In this, and later, papers the effect upon the redox potentials of complexes of a single metal by substitution of various groups into the organic ligand will be examined. This paper is concerned with iron complexes of 8-hydroxyquinolines. Most of these complexes being insoluble in water, mixed aqueous–organic solvents have to be used. The choice of solvent is limited by the solubilities of the cations, organic ligand, and salt used as background to keep the ionic strength constant. The enforced use of mixed solvents unfortunately prohibits the study of standard potentials without very detailed examination of activity coefficients, so we merely measured a series of formal potentials at equal concentrations of ferric and ferrous iron, $E_f$. Such potentials refer only to the specified conditions of solvent and ionic strength. All the formal potentials quoted here refer to three solvent systems, *i.e.*, 50% and 75% (v/v) dioxan–water and water. When these solvent systems are specified below, it must be remembered that the ionic strength was always kept constant by using 0·3M-sodium chloride as background. All redox potentials were measured against a saturated calomel electrode with a potassium chloride salt bridge. The potentials given are corrected to the aqueous hydrogen electrode, but this does not place $E_f$ on the usual hydrogen scale because its value in the dioxan-containing systems includes the differences in electrode potential between the ferric and ferrous ions *in the solvent concerned* and a liquid junction potential of unknown, constant magnitude. For example, the potential of the simple ferric–ferrous couple in 50% aqueous dioxan is +680 mv, in 75% aqueous dioxan +595 mv, and in water +690 mv. No comparison between formal potentials in different solvents is justified. However the relative potentials measured in one solvent for a series of complexes are unlikely to be much affected by changes in activity coefficient caused by minor modifications of the parent ligand molecule.

A glass electrode was used to follow changes of hydrogen-ion activity. Such measurements in mixed solvents include several unknown potentials which are functions of solvent composition. No attempt has been made to convert values to a true pH scale, and in measurements in either dioxan-containing solvent the pH-meter reading will be written p$B$.[1,2]

In the method used to examine iron–oxine couples (*i.e.*, the system ferric–ferrous–oxine) the ratio (total ferric) : (total ferrous) remained unity throughout the experiment. The p$B$ of the solution was varied by adding acid or base. After each such addition p$B$ was measured by a glass electrode. Three indicator electrodes were used to follow the changes of the formal oxidation–reduction potential, $E_f$. The results are plotted as graphs of $E_f$ against p$B$ (Fig. 2).

As the range of potential to be covered extends to about −0·3 v measurements had to to be made in the complete absence of oxygen.

[1] Van Uitert and Haas, *J. Amer. Chem. Soc.*, 1953, **75**, 451.
[2] Irving and Rossotti, *J.*, 1954, 2904.

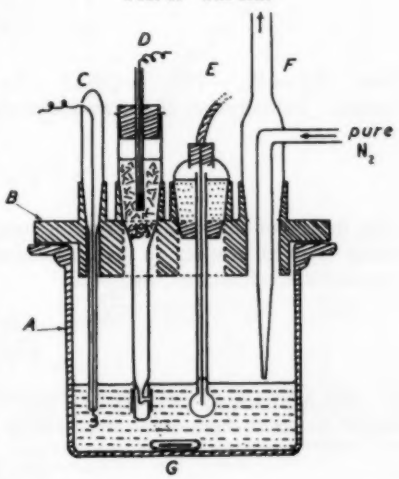
## Experimental

*Apparatus.*—The gas-tight cell *A* (Fig. 1) (volume, *ca.* 200 ml.) is a flat-bottomed cylindrical glass beaker with a wide flanged top on which rests the flanged Polythene cell-cap *B* through which "Quickfit" ground glass sockets of standard 1 : 10 taper carry three redox indicator electrodes [one gold wire, one platinum wire (*C*), one platinum foil], a glass electrode, *E*, a calomel electrode, *D*, a micrometer syringe burette, a gas lead, *F*, providing both inlet and outlet for the nitrogen (arranged so that the gas impinges on the surface of the solution, and does not bubble through it), and a spare socket. *G* is a magnetic stirrer.

When *A* and *B* are fitted together after being greased, and there is a slight positive pressure of nitrogen in *A*, no measurable amount of oxygen leaks in during 50 hr.

"Oxygen-free" nitrogen (British Oxygen Co.) being not sufficiently pure, it was passed through chromous chloride solution, then through an acid trap, and through pre-saturators of the same solvent composition and temperature as used in the cell. The entire assembly was of glass. On leaving the titration cell, the nitrogen escaped through a mercury seal into the atmosphere. The presence of oxygen in the purified nitrogen could be detected in the cell by the effect on a dilute acidified solution (M/2000) of ferrous oxine complex. At pH *ca.* 3·0 this solution is very pale yellow and oxidation to the ferric complex turns it green: the effect can be observed more accurately by use of redox electrodes.

Fig. 1. *The cell.*




The titration cell is kept at 25°. The apparent pH of the solution was measured between the calomel electrode and the glass electrode on a "Cambridge" pH-meter to ±0·02 pH unit. The redox potentials were measured between the calomel electrode and each of the three redox electrodes by using a "Pye" precision potentiometer and a "Scalamp" galvanometer, which allowed an accuracy of ±1 mv.

*Procedure.*—In strongly reducing solution the solvent, acidified with mineral acid to provide a low initial p*B*, and the required equal amounts of ferric and ferrous ions were added to the cell. Solid ligand (about 20 mg.) was placed in a tiny glass "basket" supported above the level of the liquid by a glass rod passing through an airtight gland in the cell-cap. Nitrogen was passed through for 1—2 hr. with rapid stirring, and the ligand was added to the solution by immersing the basket. Although it dissolved quickly, at least ½ hr. was allowed for equilibrium to be established before making measurements. Passage of nitrogen continued during the subsequent titration, with rapid stirring. During the initial stages there is little danger of oxidation of the ferrous ion as the potential in the solution is high (*ca.* +0·5 v). p*B* was next increased by adding small quantities of concentrated (*ca.* 3N) carbonate-free alkali from the micrometer syringe. p*B* and the redox potential were read after each addition, time being allowed for equilibria to be established. It was necessary to isolate each circuit in turn when making measurements. The usual concentration of ligand was M/700, and that of the cations M/5600.

A typical plot of $E_t$ against p*L* (= −log [ligand]) is shown in Fig. 2. In 50% dioxan and in water potentials at low p*B* values were usually slightly different for each of the three electrodes, and the spread of these early readings is shown. No reading was accepted as reversible (see below) unless all three electrodes gave the same potential to within ±10 mv. The potentials now quoted are not given to any higher accuracy except when a special experiment so demands. Although this may seem a very large error, equilibrium at low p*B* was often attained only slowly and such an error represents a compromise between experiments of very long duration and very high accuracy. At high p*B* the potentials are accurate to within 1 mv.

*Theory.*—The curves of redox potential against pH can be used to find formation functions for both ferric and ferrous complexes as follows. The concentration of a free cation [M] in the presence of ligand of concentration [L] is given by

$$[M] = \frac{T_M}{1 + K_1[L] + K_1K_2[L]^2 + K_1K_2K_3[L]^3} \quad . \quad . \quad . \quad (1)$$

where $K_1$,$K_2$, and $K_3$ refer to the successive stability constants of ML, $ML_2$, and $ML_3$ and $T_M$ is the total amount of cation.

The degree of formation is

$$\bar{n}_M = [M]\{K_1[L] + 2K_1K_2[L]^2 + 3K_1K_2K_3[L]^3\}/T_M \quad . \quad . \quad . \quad (2)$$

Differentiation of (2) with respect to [L], and conversion by appropriate operations, gives

$$\frac{d \ln [M]}{d \ln [L]} = -\bar{n}_M \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Now $[L] = T_L - [HL] - [H_2L] - \bar{n}_M T_M$, where $T_L$ is the total concentration of ligand. Substitution of the acid dissociation constants $\kappa_1$ and $\kappa_2$ gives

$$[L] = \frac{T_L - T_M \bar{n}_M}{1 + [H]/\kappa_1 + [H]^2/\kappa_1\kappa_2} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The degree of formation of proton complexes is $\bar{n}_H = ([HL] + 2[H_2L])/T_L$. Differentiating (4) with respect to [H], assuming $T_L > T_M\bar{n}_M$, substituting for $\bar{n}_H$, and carrying out suitable operations, we obtain

$$\frac{d \ln [L]}{d \ln [H]} = -\bar{n}_H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The assumption employed in deriving eqn. (5) is good providing there is excess of ligand as $\bar{n}_H$ changes much more slowly than [H]. Combining (3) and (5) we obtain

$$\frac{d \ln [M]}{d \ln [H]} = \bar{n}_M \cdot \bar{n}_H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

An equation of this form was deduced earlier in a description of the change of extraction of metal complexes with hydrogen-ion concentration.[3] Now the formation of the complexes of one cation proceeds independently of that of another cation in the same solution. Consider a metal in two valency states which are present in equal concentration

then $$E_t = E^\circ_t - (RT/F) \ln ([M^{II}]/[M^{III}]) \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where $E^\circ$ is the standard redox potential of the couple. Then

$$\frac{dE_t}{d \ln ([M^{II}]/[M^{III}])} = -\frac{RT}{F}$$

and from eqn. (6) $$\frac{dE_t}{d \ln [H]} = \frac{RT}{F} \cdot (\bar{n}_{III} - \bar{n}_{II})\bar{n}_H$$

whence at 25°C $$\frac{dE_t}{dpH} = -0{\cdot}059(\bar{n}_{III} - \bar{n}_{II})\bar{n}_H \quad . \quad . \quad . \quad . \quad . \quad (8)$$

[3] Irving, Rossotti, and Williams, *J.*, 1955, 1906.

Equation (8) has been thoroughly tested by independent measurements of $\bar{n}_{III}$ and $\bar{n}_{II}$ and of $dE_t/dpH$ or $dE_t/dpB$. Providing the two valency states form complexes over well separated regions of pH—there is little overlap in the formation of ferrous and ferric oxine complexes—then the formation functions for the two cation complexes can be completely determined and all six step constants obtained. $dE_t/dpH$ is zero for either $\bar{n}_H = 0$ or $\bar{n}_{III} = \bar{n}_{II}$. Equation (8) has been used to obtain many constants of the ferrous and ferric oxine complexes. Thus although this paper is largely concerned with redox potentials themselves these potentials can be broken down into sets of stability constants which reveal the cause of changes of potentials. We will turn to the experimental confirmation of our method first.

FIG. 2. *Oxine complexes.*

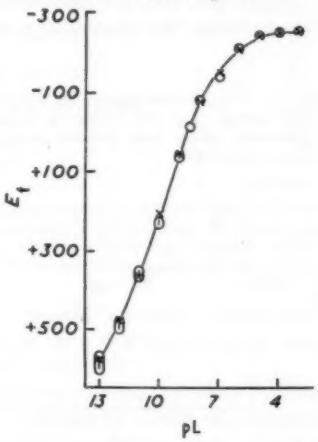
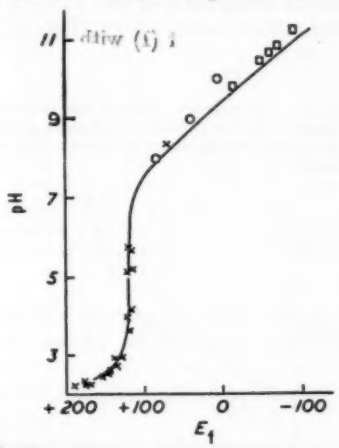



FIG. 3. *Iron–enta couples in water.*




In all Figures, $E_t$ is in mv.

The circles and ellipses are experimental points drawn so as to show the error due to different readings of the three electrodes and the crosses are those calculated from formation functions of the individual ferrous and ferric complexes (see text).

Solid line, present work (Pt electrode) with extra points, □, showing the values for the gold electrode where these differ. × Experimental potentials and ○ points calculated from Schwarzenbach and Heller.

*Results.*—We first re-examined the ferrous–ferric ethylenediaminetetra-acetic acid complexes in aqueous solution, first studied by Schwarzenbach and Heller [4] (Fig. 3). The agreement is excellent over the pH range 2·5—7·5 (in this solvent the meter readings are true pH values). When both ferric and ferrous complexes are fully formed, $dE_t/dpH$ is zero [eqn. (8)]. Above pH 8·0 there is a marked difference between the two sets of results. Our work, which is more detailed than the earlier work, shows a slope of $E_t/pH = -0{\cdot}059$, indicating that there is one hydrogen ion difference between the ferric and ferrous complexes in this region [eqn. (8)]. The ferric complex can be written $[Fe^{III}(enta)(OH)]^{2-}$. Further hydrolysis was not detected below pH 10 of either the ferric or the ferrous complex, in marked disagreement with earlier work.[4] The time involved in measurements such as ours is about one day, but the discontinuous mid-point method used originally must have taken much longer.

*Iron Oxine Complexes.*—The method was further tested with the redox potentials of the ferric–ferrous complexes of 8-hydroxyquinoline in 50% and 75% dioxan–water (Fig. 2). In the early stages of the titration (low p$B$) the ligand is present as the cation

[4] Schwarzenbach and Heller, *Helv. Chim. Acta*, 1951, **34**, 576.

$H_2$ oxine$^+$. As sodium hydroxide is added, p$B$ rises and the ligand dissociates to H oxine. This implies that $\bar{n}_H$ falls from 2·0 towards 1·0. Also in this region $\bar{n}_{III}$ is increasing while $\bar{n}_{II}$ is zero, so $\bar{n}_H(\bar{n}_{III} - \bar{n}_{II})$ is less sensitive to change in p$B$ than $\bar{n}_{III}$ alone. Hence the slope $dE_t/dpB$ (eqn. 8) changes slowly. Subsequently $\bar{n}_H$ remains unity over a wide range of p$B$ and $\bar{n}_{III}$ tends to a maximum value of 3·0. The ferrous complex begins to be formed when $2{\cdot}0 < \bar{n}_{III} < 3{\cdot}0$ and thereafter $dE_t/dpB$ decreases. At the highest p$B$ the value of $E_t$ is independent of p$B$, *i.e.*, of the hydrogen-ion concentration, and this could mean either that both ferric and ferrous complexes are at the same co-ordination stage, or that the ligand molecule is completely dissociated [eqn. (8)]. The former has been shown to be true by calculation of the degree of dissociation of the ligand acid from the known value of the acid dissociation constants, and by the study of the ferric and ferrous complexes separately by Calvin–Bjerrum titrations; these permitted a complete calculation of the form of the plot of $E_t$ against pL, and the calculated and experimental values agreed (Fig. 2). This amply demonstrates the reversibility of the

FIG. 4. *The relation between the basicity of the ligands and the oxidation–reduction potentials of the fully formed oxine complexes (for key, see Table* 1).

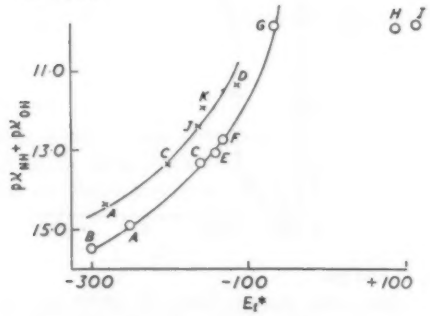
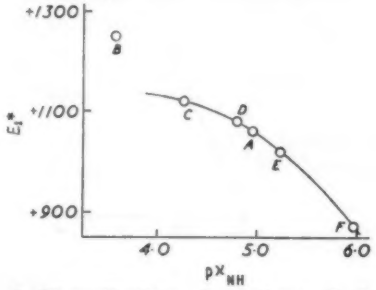



FIG. 5. *The relation between the basicity of the ligands and the oxidation–reduction potentials of the fully formed phenanthroline complexes.*




*A*, Phenanthroline; *B*, 5-nitro-; *C*, 5-chloro-; *D*, 5-phenyl-; *E*, 5-methyl-; *F*, 4 : 7-dimethyl-phenanthroline.

potentials measured. The reversibility was also confirmed, first by changing the titration procedure to one of adding acid to an alkaline solution of the complexes. Exactly the same values of $E_t$ ($\pm 2$ mv) were found over the whole pH range. Secondly, in experiments in which different total amounts of ligand were varied over a range of 1000 : 1 the expected change of redox potential was observed. Thirdly, similar tests with another ligand, 5-formyl-8-hydroxyquinoline (50% dioxan–water), also showed good reversibility of the electrodes. Finally, a correctly poised oxidation curve of ferrous 5-formyl-8-hydroxyquinoline, obtained by titration with potassium chloroiridate at a fixed p$B$, had exactly the same mid-point potential as that obtained by the continuous mid-point method.

*Hydrolysis.*—With the ferrous ion, hydrolysis does not compete with complex formation by 8-hydroxyquinolines as it starts at a much higher p$B$ (pH). In titrations of acid solutions of ferric salt by alkali in the three different solvents the hydrogen ion displaced by hydrolysis below the pH (or p$B$) at which complex formation with any oxine complex reaches $\bar{n}_{III} = 1{\cdot}0$ was found to be insignificant, and it may be that chloride protects the ferric ion. Hydrolysis was ignored in the consideration of the results.

*Potentials of* 3 : 1 *Complexes.*—At high p$B$ the complexes of the two valency states have the same composition $M(oxine)_3$. The redox potentials of the fully-formed couples $Fe^{III}(oxine)_3/Fe^{II}(oxine)_3$ of a series of substituted oxines are in Table 1. Fig. 4 shows

the result of plotting these potentials ($E_f^*$) against a preferred measure of ligand basicity [5] ($p\kappa_{NH} + p\kappa_{OH}$): these are " practical " [2] acid dissociation constants. There is no simple relation between the sum of the $p\kappa$ values and $E_f^*$. Such a relation would result if, as has often been suggested, there is a general relation between the acid dissociation constants of a series of ligands and log $K$ (stability constant) of the metal chelates of these ligands. This

TABLE 1. *Dissociation constants, stability constants, and redox potentials of iron oxine complexes.*

| Substituent in 8-hydroxyquinoline | Key for Fig. 4 | Solvent; dioxan (%) | $p\kappa_{NH}$ | $p\kappa_{OH}$ | $E_f^*$ | $\log \beta_3^{III}$ | $\log \beta_3^{II}$ |
|---|---|---|---|---|---|---|---|
| None | *A* | 50 | 4·08 | 10·82 | −251 | 38·00 | 22·13 |
| | | 75 | 3·14 | 11·22 | −283 | 37·20 | 22·23 |
| 5-methyl | *B* | 50 | 4·24 | 11·25 | −300 | (39·5) | (23·0) |
| 5-fluoro | *C* | 50 | 2·76 | 10·55 | −162 | (35·6) | (21·3) |
| | | 75 | 2·20 | 11·15 | −202 | ? | (21·1) |
| 5-ethoxycarbonyl | *D* | 50 | 2·88 | 8·72 | −102 | ? | ? |
| | | 75 | 2·00 | 9·35 | −114 | (33·7) | (21·7) |
| 5-sulphonic acid | *E* | 50 | 3·40 | 9·68 | −141 | (35·65) | (21·75) |
| 5-aldoxime | *F* | 50 | 3·52 | 9·22 | −133 | (34·0) | (20·2) |
| 7-iodo-5-sulphonic acid | *G* | 50 | 1·75 | 8·13 | −65 | (31·5) | (18·85) |
| 5-formyl | *H* | 50 | 2·51 | 7·43 | 87 | 29·5 | 19·45 |
| 5-cyano | *I* | 50 | 2·02 | 7·85 | 114 | (29·8) | (20·2) |
| 5-bromo | *J* | 75 | 1·93 | 10·45 | −163 | 35·6 | 21·41 |
| 5-iodo | *K* | 75 | 1·64 | 10·27 | −158 | 34·2 | 20·96 |

$\log \beta_3^{III}$ and $\log \beta_3^{II}$ are ferric and ferrous formation constants for 3 : 1 complexes. The values in parentheses were obtained from the slope of the redox potential with p$B$ (see text). Other values were obtained from the Bjerrum–Calvin method by using pH titration data alone. The acid dissociation constants are practical constants.[3]

was suggested for ferric phenoxides [6] and for ferrous 1 : 10-phenanthroline complexes,[7] although very few substituents were studied and the results do not obey exactly the linear relation.

A linear relation between $E_f^*$ for the ferric–ferrous 1 : 10-phenanthroline couples and $p\kappa_{NH}$ is refuted by Fig. 5, which has the same form as Fig. 4.

Marked exceptions from what can be considered to be general behaviour represented by Fig. 4 are observed with 5-formyl- and 5-cyano-oxine. The formation of the separate ferric and ferrous complexes of these ligands shows that the high potentials are attributable not only to a special stability of the *ferrous* complex, but also to destabilisation of the *ferric* complex (Table 1). When the results for 5-formyloxine complexes are compared with those for chelates of " ferron " (8-hydroxy-7-iodoquinoline-5-sulphonic acid) (both ligands have almost the same basicity) the $E_f^*$ values differ by 152 mv. The stronger ferric complexes are formed by " ferron," but with the ferrous complexes the formyloxine chelates the more strongly. Now the electronic configurations of ferric and ferrous ions in an octahedral field differ by one $d_\epsilon$ electron, and it is this that causes the properties of two valency states to differ and the $Fe^{II}$ cation to act as an electron donor and the $Fe^{III}$ as an acceptor.[8] Now the 5-formyl group is a $\pi$-electron acceptor whereas the groups in " ferron," the iodine atom and possibly the sulphonate ion also, are $\pi$-electron donors, so it is hardly surprising that the electron-donor cation should be stabilised by the electron-acceptor substituent and *vice-versa*. The two " abnormal " ligands in Fig. 4 contain strong electron-acceptor groups, formyl and cyano. The ligands which fall on the curve all contain electron-donor substituents. The quantity ($p\kappa_{NH} + p\kappa_{OH}$) being used as a measure of $\sigma$-donor strength, the change from 5-methyloxine to oxine changes $E_f^*$ much more than the same decrease in basicity caused by change from oxine to halogen-substituted oxines owing to the difference in character between the methyl group (donor

[5] Jones, Poole, Tomkinson, and Williams, preceding paper.
[6] Milburn, *J. Amer. Chem. Soc.*, 1954, **77**, 2064.
[7] Brandt and Gullstrom, *J. Amer. Chem. Soc.*, 1952, **74**, 3532.
[8] Williams, *J.*, 1955, 137.

of both σ and π electrons) and the halogens (σ acceptors, π donors). Ferric ion is made more stable than ferrous by both effects in the first case but only by the π effect in the second. The same considerations apply to the potentials plotted in Fig. 5.

It can now be appreciated why there is no simple relation between ($p\kappa_{NH} + p\kappa_{OH}$) and $E_t^*$ or even between ($p\kappa_{NH} + p\kappa_{OH}$) and the stability constants.[5] The stability of the complex of a transition-metal cation depends not only on the σ-electron density, but also on the π-electron density of the ligand. The latter is unlikely to affect pκ. If changes of substituent affect the σ-electron density of a ligand more than they affect the π-electron density, comparison of log $K$ and pκ is less likely to show the influence of the π-electron changes than comparison of $E_t^*$ and pκ. The greater sensitivity of $E_t^*$ to π-electron effects arises because it represents the difference of the logarithms of two stability constants (log $K^{III}$ − log $K^{II}$), both of which change in the same sense with changes of σ-electron density (*i.e.*, pκ) but which may well change in opposite senses because of π-electron changes. Thus measurement of oxidation–reduction potentials accentuates the effect of π-electrons.

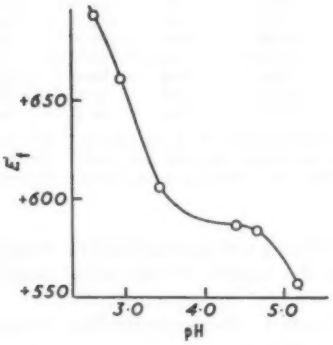



FIG. 6. *Plot of* $E_t$ *against* pH *for the 2-methylphenanthroline complexes showing that the potential becomes independent of* pH.

$E_t^*$ is also a preferable quantity to log $K$, since accurate values are obtainable *directly* by experiment.

The substituents markedly affect the absorption spectra of the ferric and ferrous complexes.[9] The interpretation of the spectra fully substantiates the suggested nature of the interaction between the substituted ligands and the cations.

*Other Oxidation–Reduction Potentials.*—*1 : 10-Phenanthroline chelates with iron.* In the 8-hydroxyquinoline complexes both the ferric and the ferrous ion have the electron configuration of the respective gas cations, although this statement requires qualification in that the visible absorption spectra of the ferrous complexes indicate that 10—30% of the ferrous ion is present in the diamagnetic form. This " promoted " electron configuration makes for greater stability of the complex than if the ion is in its ground state, although this stabilisation can hardly be measurable if the proportion of " promoted " form is below 50%. In the tris-1 : 10-phenanthroline chelates, the ferrous ion is 100% diamagnetic and covalent, and although the ferric ion is not completely in the ground state, neither is it completely in the promoted configuration.[10] The stability of the ferrous state relative to that of the ferric must therefore be much greater in phenanthroline than in oxine complexes. This is reflected by the very high oxidation–reduction potentials of the couples, +∼1·0 v.

A second demonstration of the effect of change of electron configuration upon redox potential is provided by the study of the iron 2-methylphenanthroline complexes. The redox potentials at room temperature ($E_t$), obtained by individual oxidimetric titration

[9] Tomkinson and Williams, *J.*, 1958, 1153.
[10] Williams, *Chem. Rev.*, 1956, **56**, 299.

in aqueous solutions buffered by excess of this ligand at different pH-values, are plotted against pH in Fig. 6. $E_t$ falls to +0·585 v, which is independent of pH. At this stage both valency states are present as tris-chelates, and this voltage is $E_t$*. The redox potential ($E_t$*) of the parent ferric–ferrous phenanthroline (ferriin–ferroin) couple is +1·06 v. Now ferrous 2-methylphenanthroline is paramagnetic (Irving, personal communication) and this is the only case of an iron tris-1 : 10-phenanthroline couple with a redox potential lower than that of the simple $Fe^{III}$–$Fe^{II}$ (hydrates) couple. Presumably steric hindrance prevents the stabilisation of the promoted ferrous state. These observations show that no change in ligand, other than one which brings about a change of the electron configuration of the cations, stabilises ferrous relative to ferric in aqueous solution.

The very large difference in potential between the iron–oxine and the iron–phenanthroline couples is undoubtedly due to the different entropy changes which occur on formation of complexes with anionic and neutral ligands. When neutral ligands form complexes the entropy changes are small irrespective of the cationic charge,[11] but with anionic ligands they are large and increase with cationic charge. Hence the redox potentials are lower (more negative) in the latter cases. The low potentials of the iron–oxine, –oxalate, –fluoride, and –enta couples can thus be readily understood. The iron–cyanide couple has a potential of +0·36 v which is much higher than those of the other anionic complexes. The cyanides being inner-orbital, covalent complexes, the ease of promotion of the ferrous ion also raises the redox potential somewhat.

Ahrland and Chatt [12] have discussed the ferric–ferrous pentacyano-complexes with water or ammonia in the sixth co-ordination position. They observed that the ammine had the lower redox potential and took this to confirm a generalisation that the better the electron-donor character of the ligand, the more stable the higher valency state of *covalent or inner-orbital complexes*. Although the hexacyano-complexes of ferric and ferrous iron are inner-orbital complexes, and probably the pentacyano-ammines too, there is evidence that the ferric pentacyanoaquo-ion is not.[13] There is a second objection to conclusions based on studies of complexes in which the atoms within the co-ordination sphere are changed, because the higher-valency ion state is invariably smaller than the lower, so that a change in the size of the ligand introduces steric factors. These are not important when the changes in ligand character are produced by substitution remote from the bonding centre, as with the oxine complexes (above). The second objection cannot be raised against an interpretation of the potentials of the substituted 1 : 10-phenanthroline complexes, which are covalent in the ferrous form, but as the ferric ion may well be an equilibrium mixture of ionic and covalent states, this series of complexes is not a suitable basis for a generalisation.[14] The magnetic data are indecisive. The general statement that the ferric rather than the ferrous valency state among inner-orbital complexes is stabilised by increase of electron-donor character of ligands, has been established however [15] for substituted porphyrin complexes further co-ordinated with pyridine and cyanide; magnetic evidence shows that both sets of complexes are covalent.[15] Hence there appears to be a good case for the proposition that the ferric state is stabilised relative to the ferrous state by increase in the electron-donor character of the ligands provided that *both* the ions are in either the ground or the promoted state. However the ferrous state is probably somewhat stabilised by increase in the electron-acceptor character of the ligand, no matter what the electron configuration of the cations.

There is also a class of complex in which the ferrous ion is diamagnetic (inner-orbital or covalent) whereas the ferric ion is ionic. Here the ferrous ion should be the more

[11] Williams, *J. Phys. Chem.*, 1954, **58**, 121.
[12] Ahrland and Chatt, *J.*, 1957, 1379.
[13] Simon and Knauer, *Z. Electrochem.*, 1946, **46**, 13.
[14] Gaines, Hammett, and Walden, *J. Amer. Chem. Soc.*, 1936, **58**, 1668.
[15] Martell and Calvin, " The Chemistry of the Metal Chelates," Prentice-Hall Inc., New York, 1953, p. 373.

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rapidly stabilised either by increase in the σ-donor or π-acceptor character of the ligand. Biological systems appear to contain many examples of this type of variation of redox potential with change of ligand.[10]

It seems unlikely that any generalisation might profitably be extended from iron couples to other metal systems, although Ahrland and Chatt,[12] studying covalent platinum complexes, put forward the general rule that increase in ligand donor strength, either σ or π, increases the stability of the higher valency state. This rule is considered to apply only to *covalent* complexes. For platinum complexes the rule is based on comparisons of potentials for couples of the type $L_2PtCl_4$–$L_2PtCl_2$ which can be considered as: 1, between one pair of *cis–cis* and one pair of *trans–trans* complexes; or 2, between pairs of *trans*-complexes which have different L groups. Objection can be raised to interpretation of the relative values of these potentials solely in terms of electronic effects. The difference in redox potential between the *cis–cis* and *trans–trans* couple is only 18 mv, *i.e.*, a change of *ca.* 2 in the ratio of the stability constants. The entropy changes due to statistical differences, although in the wrong direction, are of this magnitude, even if steric effects are ignored. In the comparison of the three *trans–trans* couples the ligands chosen were 4-*n*-pentylpyridine, tri-*n*-propylphosphine, and di-*n*-propyl sulphide. These differ greatly in size, so steric effects could be important, and we consider that the above generalisation needs more detailed confirmation even though it may well apply in the case of the platinum couples. A second criticism of this generalisation, deduced from the study of one set of metal complexes, applies when other cations are considered. For example, the redox potential of the cobaltic–cobaltous couple in water is +1·80 v, but the cobalt–cyanide couple has a potential less than −0·8 v. These data are to be contrasted with the potentials of the ferric–ferrous hydrate couple (+0·77 v) and cyanide couple (+0·36 v). The smaller change in the iron than the cobalt couple can be regarded as due to stabilisation of the particular electronic configuration common to both ferrous and cobaltic in inner-orbital complexes. Similarly, the difference in potential between the manganic–manganous hydrate couple (+1·50 v) and cyanide couple (+0·22 v) can be regarded as due to the lack of stability of inner-orbital complexes of manganous, as of ferric, owing to the stability of the half-filled shell. Such specific effects demand an enquiry into the individual metal couples. Moreover, the dependence of complex stability upon changes in σ or π character of the ligand, even if attention is restricted to either inner- or outer-orbital complexes, has not been sufficiently studied to allow confident predictions from the case of one metal. The cyanide couples and pyridine *meso*porphyrin couples of three cations [16] are shown for comparison in Table 2. All the complexes are of the inner-orbital type, and it is difficult to see how the differences in potential can be accounted for without reference to specific electron configurations.

TABLE 2. *Potentials in* mv.

| | $Mn^{III}$–$Mn^{II}$ | $Fe^{III}$–$Fe^{II}$ | $Co^{III}$—$Co^{II}$ |
|---|---|---|---|
| $(CN)_6$ ..... | 220 | 360 | −800 |
| *meso*Porphyrin$(pyridine)_2$ ..... | −387 | −63 | −265 |

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[*Received, August 16th,* 1957.]

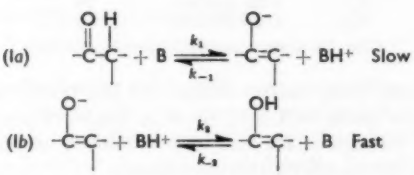
[16] Martell and Calvin, "The Chemistry of the Metal Chelates," Prentice-Hall Inc., New York, 1953, p. 377.

## 410. *Deuterium Isotope and Solvent Effects in the Base-catalyzed Keto–Enol Transformation of Methylacetylacetone (3-Methylpentane-2 : 4-dione).*

By F. A. Long and D. Watson.

The rates of bromination of methylacetylacetone (3-methylpentane-2 : 4-dione) and of its 3-deutero-analogue have been measured at 25° in water and $D_2O$ with the basic catalysts water and acetate ion. When the solvent and catalyst are the same, the monodeutero-ketone reacts about four-fold more slowly than the proton compound. With either of the catalysts the ratio of the rates of bromination of a given compound in the two solvents, $k^H/k^D$, is about 1·3. For acetate ion as catalyst this value must be due to a pure solvent effect. If the same solvent effect enters for the water-catalyzed reaction one can conclude that the base strengths of $H_2O$ and $D_2O$ are the same. Data on the keto–enol equilibrium for the two solvents permit calculations of the rates of the reverse, ketonization reactions. Since the mechanism of this reverse reaction is known, one can also calculate rate ratios for the slow acid-catalyzed formation of ketone from the enolate ion. The interesting result is that the $k^H/k^D$ ratio for catalysis by acetic acid is about 6. Combination of these and related data permits a detailed analysis of the acid–base properties of $H_2O$ and $D_2O$ and their ions.

Measurement of relative rates in the solvents $D_2O$ and $H_2O$ is frequently utilized in studies of the mechanisms of acid and base catalysis and data are available for a variety of reactions.[1,2] Even so, there is still a lack of data for reactions of known mechanism and this is perhaps the more serious for catalysis by bases. In this paper we present results for the reversible, base-catalyzed transformation of ketones into enols. The mechanism for this reaction is quite firmly established as:[3,4]




It is usual to follow reaction (I*a*) by measuring the rate of halogen uptake, since the enolate ion which is formed is halogenated almost instantaneously. The reaction is subject to general base-catalysis and rate data are available for a variety of ketones and catalysts.[5,6,7] A few studies of hydrogen-isotope effects have also been reported. Reitz and Kopp [8] showed that the reaction of [6-$^2$H]acetone in aqueous solution, catalyzed by acetate ion, was about 7-fold slower than that of ordinary acetone. (A similar ratio also holds for catalysis in ordinary water by the acids acetic and hydrogen ion.) The bromination of acetone, catalyzed by acetate ion, is 1·15 times faster in $H_2O$ than in $D_2O$.[8] This must be a pure " solvent effect " since both the reactant and the catalyst are identical for the two solvents.

Nachod [9] has studied both the rate of bromination of the ketone and the keto–enol

[1] Bell, " Acid-Base Catalysis," Oxford Univ. Press, 1941, Chap. VII.
[2] Wiberg, *Chem. Rev.*, 1955, **55**, 713.
[3] Hammett, " Physical Organic Chemistry," McGraw Hill Book Co., New York, 1940, Chap. IV.
[4] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Chap. X, 1953.
[5] Dawson and his co-workers, *J.*, 1929, 1884, and earlier.
[6] Pederson, *J. Phys. Chem.*, 1934, **38**, 999, and earlier.
[7] Bell and his co-workers, *Proc. Roy. Soc.*, 1949, *A*, **197**, 308, and earlier.
[8] Reitz and Kopp, *Z. phys. Chem.*, 1939, *A*, **184**, 429.
[9] Nachod, *Z. phys. Chem.*, 1938, *A*, **182**, 193.

equilibrium for the β-diketone, 3-methylacetylacetone, in solutions of hydrochloric acid in $H_2O$ and $D_2O$. The kinetic data were reported to be for catalysis by hydrogen ion, but it is now known that they are really for base catalysis by the solvent water since this and similar β-diketones show only base-catalyzed enolization.[10,11] Nachod's results are not directly comparable with those for acetone since his kinetic data are actually for the hydrogen compound in water and for the monodeutero-compound, $CH_3{\cdot}CO{\cdot}CDMe{\cdot}CO{\cdot}CH_3$, in $D_2O$, *i.e.*, for the " equilibrated " mixtures.

3-Methylacetylacetone is a favourable compound for study because only one hydrogen atom is normally replaced by bromine (or by deuterium), and because it is possible to obtain data for both the forward and the reverse reactions. We have consequently repeated Nachod's measurements and have extended them to include other catalysts and other reactions. Table 1 summarizes the kinetic results for the bromination of the ketone. In this and in subsequent discussions the symbol KH is used for the protonated ketone and KD for the ketone which has the single active hydrogen atom replaced by deuterium (similarly ED will refer to the enol with the hydroxyl hydrogen replaced by D). Finally, the solvents $H_2O$ and $D_2O$ are indicated by the superscripts H and D respectively. The $k_1$ values of Table 1 are for the second-order reaction of ketone and catalyst; those for acetate ion are calculated after subtraction of the contribution of the water reaction to the observed rate.

TABLE 1. *Rate of bromination of methylacetylacetone in* $H_2O$ *and* $D_2O$ *at* 25°.

| No. | Reactant | Solvent | Catalyst | $k$, obs. (sec.$^{-1}$ × $10^5$) | $k_1$, calc.[a] (l. mole$^{-1}$ sec.$^{-1}$ × $10^5$) |
|---|---|---|---|---|---|
| 1 | KH | $H_2O$ | $H_2O$ | 9·6 | 0·173 |
| 2 | KH | $D_2O$ | $D_2O$ | 7·0 | 0·126 |
| 3 | KD | $H_2O$ | $H_2O$ | 2·75 | 0·049 |
| 4 | KD | $D_2O$ | $D_2O$ | 2·1 | 0·038 |
| 5 | KH | $H_2O$ | 0·2M-NaOAc | 155 | 725 |
| 6 | KH | $D_2O$ | 0·2M-NaOAc | 123 | 580 |
| 7 | KD | $H_2O$ | 0·2M-NaOAc | 28 | 125 |
| 8 | KD | $D_2O$ | 0·2M-NaOAc | 23 | 104 |

[a] Calc. for water catalysis from $k_1 = k/55{\cdot}5$.

Information is available from earlier studies for reactions 1 and 4 of Table 1. Our results for reaction 1 agree fairly well with those of Nachod [9] and of Pearson and Mills.[11] However, for reaction 4, Nachod's data lead to $k = 0{\cdot}00004$, which is twice as large as our value. We do not know the reason for this discrepancy.

The data of Table 1 lead to the following ratios for the reaction of KH in the two solvents:

$$(k^H/k^D)_{H_2O} = 1{\cdot}37 \text{ and } (k^H/k^D)_{OAc^-} = 1{\cdot}25$$

The ratio for the acetate ion as catalyst is similar to that reported for the bromination of acetone [8] and again indicates that the pure " solvent effect " leads to slightly faster reaction in $H_2O$ than in $D_2O$. It is then of considerable interest that virtually the same ratio is observed for catalysis by water as by acetate ion. Since ratios of close to 1·3 are also found for reaction of the monodeutero-compound with the two catalysts, it seems safe to conclude that this value represents a general solvent effect for the reactions of ketones in $H_2O$ as compared with those in $D_2O$.

The other ratios of interest are those for reaction of the ordinary and deuterated ketones. For reaction in the same solvent, ordinary water, these are:

$$(k^H{}_{KH}/k^H{}_{KD})_{H_2O} = 3{\cdot}5 \text{ and } (k^H{}_{KH}/k^H{}_{KD})_{OAc^-} = 5{\cdot}8$$

Ratios for reaction in the solvent $D_2O$ are essentially the same as these. Since the reaction involves rupture of a carbon–hydrogen bond, these large ratios are the expected

[10] Bell and Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88.
[11] Pearson and Mills, *J. Amer. Chem. Soc.*, 1950, **72**, 1692.

result. They are in fact quite similar to those found for related systems.[2,8] The substantial difference in the ratios for the catalysts water and acetate ion is unexpected but appears to be real.

For some purposes it is useful to have the related ratios for the " equilibrated " systems, *i.e.*, for reaction of KH in $H_2O$ relative to that of KD in $D_2O$. The values are

$$(k^{H}_{KH}/k^{D}_{KD})_{H_2O} = 4{\cdot}6 \text{ and } (k^{H}_{KH}/k^{D}_{KD})_{OAc^-} = 6{\cdot}9$$

They are slightly larger than the previous values because they include both the above isotope effect and the previously discussed solvent effect.

Two chemical equilibria are involved in this keto–enol reaction. One is that for ionization of the enol as an acid. For the enol in water the value of $K^{H}_{EH}$ is given as $5 \times 10^{-10}$ by Pearson and Mills.[11] The ionization constant for the deutero-enol (ED) in $D_2O$ has not been measured but on the basis of the data from studies with both carboxylic acids [12] and phenols [13] it is reasonable to assume that the ratio $K^{H}_{EH}/K^{D}_{ED}$ is approximately 3. The other equilibrium of interest is the overall equilibrium between the keto- and the enol form. Table 2 gives available data for the two solvents.

TABLE 2. *Values of* $K_{eq} = C_{enol}/C_{ketone}$ *for methylacetylacetone at* 25°.

| Source | $\frac{C_{EH}}{C_{KH}}$ (in $H_2O$) | $\frac{C_{ED}}{C_{KD}}$ (in $D_2O$) | $K^{H}_{eq}/K^{D}_{eq}$ |
|---|---|---|---|
| Nachod [9] | 0·0373 | 0·0254 | 1·5 |
| Schwarzenbach *et al.*[14] | 0·028 | — | — |
| Pearson [11] | 0·032 | — | — |
| This research | 0·037 | 0·025 | 1·5 |
| This research | — | — | 1·25 [a] |
| Best values | 0·034 | 0·025 | 1·35 [b] |

[a] From spectroscopic comparison of the equilibrium solutions; see experimental. [b] From the quoted best values for $K^{H}$ and $K^{D}$.

The overall equilibrium constant can be written

$$K_{eq} = C_{enol}/C_{acetone} = k_t/k_{-t}$$

where $k_t$ and $k_{-t}$ are the second-order rate coefficients for reaction of ketone with catalyst and of enol with catalyst respectively. In terms of mechanism (I), $k_t$ is identical with $k_1$ whereas $k_{-t}$ involves both $k_{-1}$ and the equilibrium constant for step (I*b*). Value of the overall coefficient $k_{-t}$ can, however, be calculated directly from the $k_1$ and $K_{eq}$ values of the previous tables, and data for the four reactions for which calculations can be made are listed below:

| Reaction | $10^5 k_{-t}$ (l. mole$^{-1}$ sec.$^{-1}$) | $k^{H}_{EH}/k^{D}_{ED}$ |
|---|---|---|
| EH + $H_2O$ (in $H_2O$) | 5·1 | 3·4 |
| ED + $D_2O$ (in $D_2O$) | 1·5 | |
| EH + $OAc^-$ (in $H_2O$) | 21,000 | 5 |
| ED + $OAc^-$ (in $D_2O$) | 4200 | |

For the ketonization, just as for reaction of the " equilibrated " ketones, the $k^{H}_t/k^{D}_t$ ratios are considerably greater than unity and not very dependent on strength of catalyst.

It seems reasonable to conclude that for general base-catalysis, independently of whether there is a one-step slow proton removal or whether a pre-equilibrium proton-transfer is involved, there will be no significant dependence of $k^{H}/k^{D}$ ratio on base strength for bases of the weakness of acetate ion and water. It remains to be seen whether there will be a change in ratio for catalysis by the strong base $OH^-$. However, the fact that $(k^{H}/k^{D})_{OH^-}$ for the base-catalyzed ionization of nitroethane and nitropropane at 5° is not far from unity [15] at least suggests that there will be no great change.

[12] Rule and LaMer, *J. Amer. Chem. Soc.*, 1938, **60**, 1981.
[13] Martin and Butler, *J.*, 1939, 1366.
[14] Schwarzenbach and Felder, *Helv. Chim. Acta*, 1944, **27**, 1701.
[15] Maron and LaMer, *J. Amer. Chem. Soc.*, 1938, **60**, 2588.

In sharp contrast to the situation for base-catalysis, there is good reason to believe that for general acid-catalysis the relative rates in $H_2O$ and $D_2O$ will depend markedly on the strength of the catalyst.[16] For a pre-equilibrium proton-transfer this expectation is particularly easy to justify and is, in addition, borne out by experiment. However, for a one-step slow proton-transfer, which is the obvious alternative mechanism for general acid-catalysis, the situation is considerably less certain. It is therefore of some importance that acceptance of the validity of mechanism (I) guarantees that an acid-catalyzed slow proton-transfer enters for the slow step of the reverse reaction. Furthermore, the available data permit calculation of the individual $k_{-1}$ values for this step, *i.e.*, for the reverse of reaction (I*a*), and also of the $k^H/k^D$ ratios. From the mechanism it follows that the ratios for the two catalysts are given by

$$(k^H_{E^-}/k^D_{E^-})_{H_3O^+} = (k^H_{KH}/k^D_{KD})_{H_3O}(K^D_{eq}/K^H_{eq})(K^D_{ED}/K^H_{EH})$$

$$(k^H_{E^-}/k^D_{E^-})_{HOAc} = (k^H_{KH}/k^D_{KD})_{OAc^-}(K^D_{eq}/K^H_{eq})(K^E_{ED}/K^H_{EH})(K^H_{HOAc}/K^D_{DOAc})$$

All but one of the ratios on the right side of these equations are known and for this one the assumption that $K^H_{EH}/K^D_{ED} = 3$ is highly plausible. However, it is worth emphasizing that if one wishes the " ratio of the ratios " (to determine the dependence of ratio on strength of catalyst) the only terms which enter are the ratio of rate coefficients for KH relative to KD and the relative ionization of acetic acid in $H_2O$ and $D_2O$. Both of these are quite firmly established.

TABLE 3. *Results for acid catalysis by one-step slow proton-transfer.*

| Values of $k_{-1}$ (l. mole$^{-1}$ sec.$^{-1}$) | Ratios |
|---|---|
| $k^H_{E^-+H_3O^+} = 5{\cdot}6 \times 10^6$ ..... | $(k^H_{E^-}/k^D_{E^-})_{H_3O^+} = 1{\cdot}1$ |
| $k^D_{E^-+D_3O^+} = 5{\cdot}0 \times 10^6$ ..... | |
| $k^H_{E^-+HOAc} = 7{\cdot}3 \times 10^3$ ..... | $(k^H_{E^-}/k^D_{E^-})_{HOAc} = 5{\cdot}6$ |
| $k^D_{E^-+DOAc} = 1{\cdot}3 \times 10^3$ ..... | |

The important conclusion is that for this slow proton-transfer, just as for a mechanism with a pre-equilibrium proton-transfer, the $k^H/k^D$ ratio is considerably larger for catalysis by a weak acid than for catalysis by the solvated proton. The further conclusion is that the binding of a proton to a weak base species such as acetate ion is of a considerably different character from that which binds the proton from a strong acid to the solvent. In this sense it may be somewhat misleading to utilize the specific formula $H_3O^+$ for the latter species.

The $k^H/k^D$ ratio in Table 3 for catalysis by hydronium ion lends support to the expectation that studies with this catalyst can aid in determining mechanisms of general acid-catalysis. For a mechanism with a pre-equilibrium proton-transfer, and where the hydrogen atom which is ultimately removed does not exchange rapidly with the solvent, one can expect the $(k^H/k^D)_{H_3O^+}$ ratio to be considerably less than unity. (An example is the acid-catalyzed bromination of acetone for which this ratio is 0·45.[3]) For a mechanism with a one-step slow proton-transfer the usual assumption is that $(k^H/k^D)_{H_3O^+}$ will be unity or slightly greater, but no data have been available for reactions of established mechanism. The ratio in Table 3 provides an example and is in agreement with the usual assumption.

One of the most interesting aspects of the data of Tables 2 and 3 is their bearing on the properties of the solvents $H_2O$ and $D_2O$. The self-dissociation of water can be conventionally written as $H_2O + H_2O = H_3O^+ + OH^-$. It is well known that the ion product for $H_2O$ is about 6-fold larger than that for $D_2O$ and there have been frequent speculations on the origin of this difference. The present kinetic data show that it is *not* due to a difference in base strength between $H_2O$ and $D_2O$. Similar kinetic data for catalysis by hydroxide ion make it unlikely that there is any large difference in the base strengths of $OH^-$ and $OD^-$ ions. Finally, the analysis of the rates of formation of ketone from enolate ion indicates that the acids $H_3O^+$ and $D_3O^+$ are of virtually the same acid strength. The implication then is that the large difference in the ion products must be

[16] Long and Bigeleisen, unpublished work.

almost entirely due to a difference in acid strength of $H_2O$ compared to $D_2O$. This is not an unreasonable conclusion and is consistent both with expectations from a general analysis along lines developed by Bigeleisen [17] and with the herein reported difference in catalytic effectiveness of another pair of weak acids, HOAc and DOAc.

## Experimental

The 3-methylpentane-2 : 4-dione was prepared by Renfrow and Renfrow's procedure.[11, 18] Fractionation of the yellow original product led to a pure colourless liquid (b. p. 172—174°; $n_D^{20}$ 1·4440). A slow deterioration occurs on storage, since the yellow colour returns and, simultaneously, the material when dissolved in water gives a considerably more acidic solution than does the freshly prepared material. This decomposition is greatly retarded if the material is stored in the cold. There is no evidence that the decomposition products interfere with the kinetics, since identical rates were obtained from studies with fresh and old material.

The monodeutero-compound, 3-deutero-3-methylpentane-2 : 4-dione, was prepared by shaking the normal compound with a large excess of $D_2O$ for several days, followed by extraction with light petroleum and then a second equilibration with $D_2O$. Examination in a mass spectrometer showed that only one of the ten possible hydrogen atoms had been replaced by deuterium, and this can safely be assumed to be the active 3-hydrogen atom. For the particular case of reaction in $D_2O$ as solvent, the kinetic behaviour of this prepared compound was identical with that of the normal compound after equilibration.

Rates of reaction of the ketones were measured by following the rate of uptake of bromine with a " Unicam " spectrophotometer. This was done by measuring the change in optical density of the reaction mixture at 3900 Å. The reactions were carried out in the spectrometer, optical cells of 1 cm. path length being used. These were mounted in a cell holder in a thermostat which was kept at 25° ± 0·05°.

For most studies of the acetate-ion catalysis and for a few experiments on the water reaction, the starting concentrations of ketone and bromine were comparable (normally a slight excess of bromine) and of the order of 0·004 mole per l. When the reactants were mixed there was an initial very rapid reaction of the enol form of the material. This was followed by a typical first-order reaction of the ketone, *i.e.*, with a rate which was independent of bromine concentration. For most of the measurements on the water reaction a large excess of ketone was used, roughly 0·04M-compound to 0·001M-bromine. This gave zero-order kinetics; the desired first-order rate coefficient was calculated from the known initial concentration of ketone.

For the reaction of ketone with acetate ion it was found that there was a slow zero-order uptake of bromine after the calculated end of reaction was reached. Similar behaviour has been found by other investigators of the reactions of β-diketones and is presumably due to the entrance of a slow side reaction.[19] It was assumed that this side reaction also occurred during the period of the normal bromination and appropriate corrections were made before calculating the rate coefficients.

All of the rate studies used for comparisons were made at ionic strength 0·2. The acetate-ion catalyst was added as sodium acetate, and the water reaction was normally studied in the presence of 0·05M-sulphuric acid and 0·15M-sodium chloride. In a few studies reactions were carried out with much higher concentrations of acid ranging up to 5M. There was virtually no change in the first-order rate coefficient, showing both that there is no acid catalysis and that the rate of the water reaction is not perceptibly influenced by the concentration of electrolyte.

Studies by Bell and his co-workers [20] on the base-catalyzed hydrolysis of several very similar β-diketones have shown that catalysis by hydroxide ion is not normally detectable at pH values smaller than 7. In the present case, all studies of acetate catalysis have been made in buffered solutions with acetate-ion concentrations of 0·2M or higher and with pH values of less than 5. Hence any contribution to the rate from a reaction with hydroxide ion can be safely ruled out. The results of a few approximate rate measurements with varying buffer ratios were in accord with this conclusion.

The accuracy of the kinetic results is best assessed by noting their reproducibility.

[17] Bigeleisen, *J. Chem. Phys.*, 1949, **17**, 675.
[18] Renfrow and Renfrow, *J. Amer. Chem. Soc.*, 1946, **68**, 1801.
[19] Bell and Gelles, *Proc. Roy. Soc.*, 1951, *A*, **210**, 310.
[20] See especially: (*a*) Ref. 8; (*b*) Bell, *Trans. Faraday Soc.*, 1943, **39**, 253; (*c*) Bell, Gelles, and Möller, *Proc. Roy. Soc.*, 1946, *A*, **186**, 443.

Reference to Table 1 shows that all the rate coefficients (except for reactions 1 and 4) are easily reproducible to within 4%. In the case of reactions 3 and 8 both first-order and zero-order techniques were used and gave similar results. Wider deviations were found in the case of reactions 1 and 4. Ten determinations of the first-order rate constant for reaction 1 gave a mean value of $9{\cdot}6 \times 10^{-5}$ sec.$^{-1}$, and there was a mean deviation of $0{\cdot}6 \times 10^{-5}$ sec.$^{-1}$. The deviation among the results for reaction 4 was similar and the mean of eight determinations is given.

The data relating to the equilibrium between keto- and enol forms have been suplemented in two ways. First, Nachod's measurements [9] on this equilibrium have been repeated. An excess of bromine was added to an equilibrated aqueous solution of the compound, kept at 0° to inhibit reaction of the keto-form. After 1 min. (to permit complete bromination of the enol), the bromine remaining was estimated by addition of potassium iodide and titration of the liberated iodine with sodium thiosulphate solution. The experiment was repeated with a solution of the deutero-compound in $D_2O$. Secondly, the ratio of the keto–enol equilibrium constants in $H_2O$ and $D_2O$ was estimated directly by comparing extinction coefficients of the hydrogen- and deutero-compound in $H_2O$ and $D_2O$ respectively at 2900 Å. The absorption which occurs at this wavelength is due to the enol content.[21] It may be shown that the ratio of the extinction coefficients is related to the equilibrium constants in $H_2O$ and $D_2O$ as follows:

$$\frac{\varepsilon^{H}_{E}}{\varepsilon^{D}_{E}} = \frac{C^{H}_{E}}{C^{D}_{E}} = \left(\frac{K^{H}_{eq}}{K^{D}_{eq}}\right) \times \left(\frac{1 + K^{D}_{eq}}{1 + K^{H}_{eq}}\right)$$

In this case both equilibrium constants are very small and so the second ratio on the right-hand side approximates to unity. The ratio of the equilibrium constants is therefore simply the ratio of the extinction coefficients.

We are indebted to Professor C. K. Ingold and Dr. Y. Pocker for helpful discussions. One of us (F. A. L.) also expresses his deep appreciation for the many privileges extended him by University College.

William Ramsay and Ralph Forster Laboratories, University College, Gower Street, London, W.C.1.
[Permanent address: Dept. of Chemistry, Cornell University, Ithaca, New York.] [*Received, October 28th*, 1957.]

[21] Grossman, *Z. phys. Chem.*, 1924, **109**, 305.

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## 411. *The Constitution of Yohimbine and Related Alkaloids. Part X.* The Synthesis of Some* 12H-*Indolo*[2 : 3-a]*pyridocolinium Salts, including Flavocoryline and Flavopereirine.*

By K. B. Prasad and G. A. Swan.

A synthesis is described of 12*H*-indolo[2 : 3-*a*]pyridocolinium salts (II), the chromophore of sempervirine. As well as the parent compound, derivatives (XI) have been prepared in which R = H, Et, and Pr$^{i}$. Of these, the first two were identical with flavopereirine and flavocoryline respectively, but it was not possible to establish the identity of the third with flavocorynanthyrine. 3-Ethyl-2-(5-ethyl-4-*iso*propyl-2-pyridyl)indole (XV; R = Pr$^{i}$), a homologue of alstyrine, has also been synthesised.

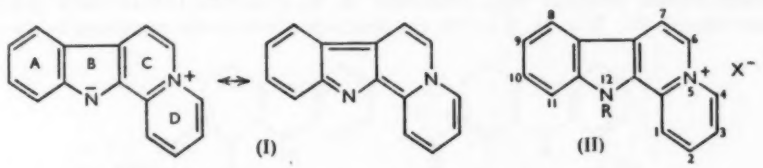
This and the following paper are concerned with a new synthetic route to rings A, B, C, and D of the yohimbine skeleton, with or without ring E. First, we synthesised the parent compound in the lowest possible state of hydrogenation and without substituents, *i.e.*, indolo[2 : 3-*a*]pyridocoline (I) [the salts being 12*H*-indolo[2 : 3-*a*]pyridocolinium salts (II; R = H)], the chromophore of sempervirine. This is here represented as a resonance hybrid of the covalent and the dipolar form, although Paolini and Marini-Bettolo [1] have

* Part IX, Lee and Swan, *J.*, 1956, 771.

[1] Paolini and Marini-Bettolo, *Nature*, 1957, **179**, 41.

recently suggested that such anhydronium bases can be adequately represented by a purely covalent structure.

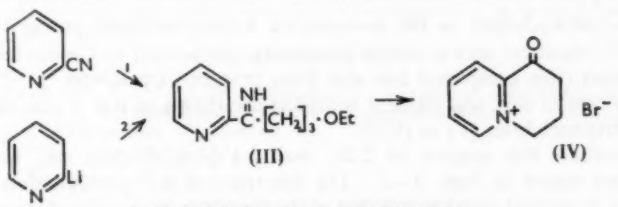
An earlier attempt by Bentley, Stevens, and Thompson (see Stevens [2]) to synthesise compound (I) failed, although the method used succeeded when a protective benzyl group



(I) (II)

was present, giving the derivative (II; R = $CH_2Ph$). The latter compound has, however, apparently not been debenzylated.

Craig,[3] describing the preparation of 2-γ-ethoxybutyrylpyridine by the action of 3-ethoxypropylmagnesium bromide on 2-cyanopyridine, stated that the product was hydrolysed by 17% hydrochloric acid and ammonium chloride solution, apparently in the cold. We carried out a similar reaction except that we used excess of the Grignard reagent (thus obtaining a somewhat higher yield) and heated the product for 20 min. with



(III) (IV)

1, Br·Mg·$[CH_2]_3$·OEt. 2, NC·$[CH_2]_3$·OEt.

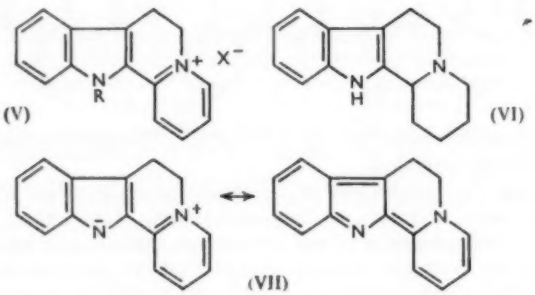
2N-sulphuric acid at 100°. Our product was, however, the imine (III) rather than the ketone, as shown by analysis and a strong absorption band at 3376 $cm.^{-1}$ (N–H). A band was also present at 1681 $cm.^{-1}$, but we were unable to decide whether this would be due to C=O or C=N. The use of hydrochloric acid gave a product which was essentially the same. For both our purposes and those of Craig it would be immaterial whether the ketone or imine was obtained. Craig converted his material into an oxime and our product gave the 2 : 4-dinitrophenylhydrazone of the expected ketone. The next step in our synthesis involved refluxing the ketone or imine with hydrobromic acid in acetic acid, after which there was no doubt that the imine had been hydrolysed. From this reaction we had expected to obtain the hydrobromide of 2-γ-bromobutyrylpyridine; but evaporation of the solution yielded a crystalline product, m. p. 205° (decomp.), which was clearly a quaternary salt and proved to be 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide (IV). As cyclisation could scarcely occur in the strongly acidic reaction mixture, it seems that it must have happened during evaporation of the solution.[4] More than a year after we had prepared this compound, Glover and Jones [5] described the preparation of the same compound (for which they give m. p. 197°) in a similar way, except that they carried out the final cyclisation in chloroform and do not comment on Craig's alleged ketone.

We also investigated certain variants on the first stage of the synthesis. Attempts to use 3-phenoxypropyl bromide for the preparation of a Grignard reagent were unsuccessful, magnesium bromide being precipitated.[6] Use of 3-ethoxypropyl-lithium was also examined, but this reagent was obtained in only low yield by the action of lithium on the bromide in

[2] Stevens, *Chem. Soc. Special Publ.*, No. 3, 1955, p. 19.
[3] Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 1144.
[4] Cf. Wieland and Neeb, *Annalen*, 1956, **600**, 161.
[5] Glover and Jones, *Chem. and Ind.*, 1956, 1456.
[6] Cf. Winterfeld and Holschneider, *Ber.*, 1933, **66**, 1751.

ether. The action of 2-pyridyl-lithium on γ-ethoxybutyronitrile however provided an alternative route, although the yield was somewhat lower than that from the method first described, and the use of γ-phenoxybutyronitrile was even less successful.

Ethanolic hydrogen chloride cyclised the phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide with formation of 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride (V; R = H, X = Cl), the structure of which was confirmed by absorption



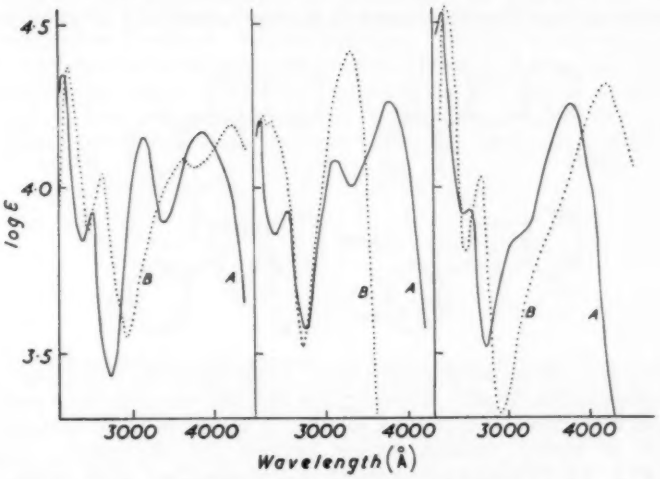

of three mols. of hydrogen in the presence of Adams catalyst, giving the octahydro-compound (VI), identical with a sample previously synthesised by Groves and Swan [7] by a different method (this compound has also been prepared by Keufer [8]). The ultraviolet absorption spectra in acid and alkaline solutions are shown in Fig. 1 and correspond with a change in structure from (V) to (VII).

For comparison the spectra of 2-2′- and 2-4′-pyridylindole and their respective methiodides are shown in Figs. 2—5. The spectrum of 2-2′-pyridylindole was identical in alkaline and in neutral solution and that of the corresponding methiodide was identical in acid and in neutral solution. The same applies to the 4′-pyridyl compounds. The alkaline spectra of the two bases resembled that of 2-phenylindole.[9] In acid solution the possibility of resonance involving structures (VIII and VIIIa; R = H or Me) is introduced and the spectrum of 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride is then rather similar to that of 2-2′-pyridylindole and of the methiodide of the latter, although the intensity of the band at 3140 Å diminishes in the order in which these three compounds are mentioned, probably owing to diminishing coplanarity. (For alstyrine, in acid solution, this band is represented by only a shoulder.) The spectra of 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride and 2-2′- and 2-4′-pyridylindole methiodide in alkaline solution suggest that all three compounds may yield anhydronium bases, although Gray and Archer [10] did not consider that their electrometric titrations pointed to this in the last case. The possibility, however, that this compound may exist in alkaline solution as a pseudo-base rather than an anhydronium base (IX) is not excluded.

That the change in structure which compound (V) undergoes in alkaline solution depends on the hydrogen atom attached to the indole-nitrogen atom was shown as follows. Addition of concentrated aqueous sodium hydroxide to a solution of the chloride gave a bright red solid, which, when treated with methyl iodide, yielded 6 : 7-dihydro-12-methyl-12*H*-indolo[2 : 3-*a*]pyridocolinium iodide (V; R = Me, X = I), identical with that obtained by a Fischer indole reaction on the 1-methyl-1-phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide. The spectrum of this compound was almost identical with that of the chloride (V; R = H, X = Cl) in acid solution, and did not change on addition of alkali.

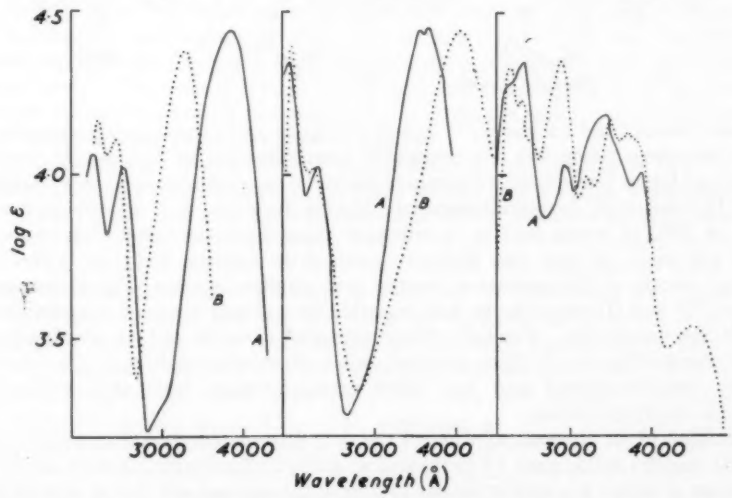
[7] Groves and Swan, *J.*, 1952, 650.
[8] Keufer, *Ann. pharm. franç.*, 1950, **8**, 816.
[9] Carlin, Wallace, and Fisher, *J. Amer. Chem. Soc.*, 1952, **74**, 990.
[10] Gray and Archer, *ibid.*, 1957, **79**, 3554.

FIG. 1. FIG. 2. FIG. 3.



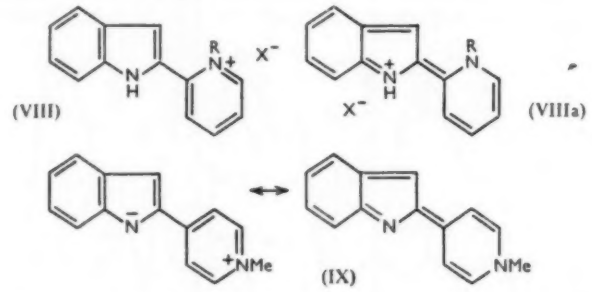

*Absorption spectra of*: FIG. 1, 6 : 7-*dihydro*-12H-*indolo*[2 : 3-a]*pyridocolinium chloride* (*A, acid or neutral*; *B, alkaline*); FIG. 2, 2-2′-*pyridylindole* (*A, acid*; *B, neutral or alkaline*); FIG. 3, 2-2′-*pyridylindole methiodide* (*A, acid or neutral*; *B, alkaline*).

FIG. 4. FIG. 5. FIG. 6.

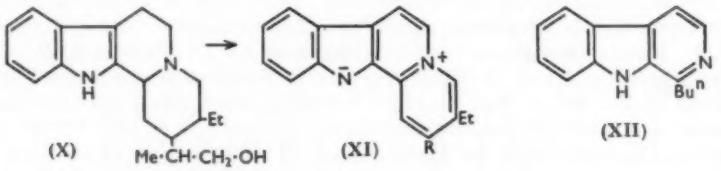



*Absorption spectra of*: FIG. 4, 2-4′-*pyridylindole* (*A, acid*; *B, alkaline or neutral*); FIG. 5, 2-4′-*pyridylindole methiodide* (*A, acid or neutral*; *B, alkaline*); FIG. 6, 12H-*indolo*[2 : 3-a]*pyridocolinium chloride* (*A, acid or neutral*; *B, alkaline*).

We had thought that dehydrogenation of **6 : 7**-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride would be effected readily since Schwyzer [11] had shown that a compound of structure (X) (obtained by degradation of corynantheine), when heated with acidic palladium–charcoal, was dehydrogenated to flavocorynanthyrine to which he attributed




structure (XI; R = Et or, less probably, Pr$^i$). However, in the case of our compound, a similar dehydrogenation failed. Moreover, the chloride was recovered unchanged after being refluxed with chloranil in butanol solution or shaken in acetic acid with oxygen in the presence of freshly reduced Adams catalyst (no absorption). Also, heating **1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b**-octahydroindolo[2 : 3-*a*]pyridocoline with acidic palladium–charcoal yielded a product thought to be 1-butyl-β-carboline (XII) as its solution in acids showed a blue-violet fluorescence at great dilution and its ultraviolet spectrum closely resembled that recorded for β-carboline by Spenser.[12]



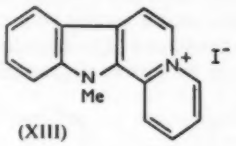

Braude, Brook, and Linstead's [13] systematic study of the use of high-potential quinones for dehydrogenation has not previously been extended to heterocyclic compounds. However, we found tetrachloro-*o*-benzoquinone to be very effective and this enabled us to prepare 12*H*-indolo[2 : 3-*a*]pyridocolinium chloride from its **6 : 7**-dihydro-derivative by reaction at 100° in acetic acid or in refluxing ethanol (in the latter case excess of the quinone was used, as part was probably used up in reaction with the solvent). The absorption spectra of the product in neutral and alkaline solution (Fig. 6) correspond to structures (II) and (I) respectively, and resemble very closely those of sempervirine under corresponding conditions. The fully dehydrogenated chloride and its dihydro-derivative show a striking difference in dilute solution under ultraviolet irradiation, the former being brilliantly blue-fluorescent and the latter greenish-yellow (this applies also to the homologues described below).

Basification of an aqueous solution of the dehydrogenated chloride yielded a product which with methyl iodide gave 12-methylindolo-12*H*-[2 : 3-*a*]pyridocolinium iodide (XIII), the spectrum of which was rather similar to that of the original salt (II) in neutral solution, but was little changed in the presence of alkali, except that the band at 2930 Å slowly disappeared on storage. This was thought to indicate the slow formation of a pseudo-base

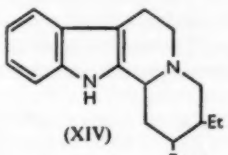
[11] Schwyzer, *Helv. Chim. Acta*, 1952, **35**, 867.
[12] Spenser, *J.*, 1956, 3659.
[13] Braude, Brook, and Linstead, *J.*, 1954, 3569.

in alkaline solution (compare the case of 7 : 8-dihydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride in the following paper, where a band at 2810 Å disappears in alkaline solution).

We also synthesised 2 : 3-diethylindolo[2 : 3-*a*]pyridocoline (XI; R = Et) by a similar route to the above from 2-cyano-4 : 5-diethylpyridine. This was of interest because it had the structure suggested for flavocoryline by Goutarel, Janot, and Perezamador y Barron [14] and for flavocorynanthyrine by Schwyzer,[11] although the last author admitted that his compound might be 3-ethyl-2-*iso*propylindolo[2 : 3-*a*]pyridocoline (XI; R = Pr$^i$). Moreover, a compound believed to have structure (XIV) has been obtained by Janot and



(XIII)



(XIV)

Goutarel [15] by degradation of corynantheine and we hoped it might be possible to cast light on the stereochemistry of the alkaloid by studying the stereospecific hydrogenation of our synthetic compound, but unsuccessfully. In surprising contrast to the lower homologue, both 2 : 3-diethyl-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride and its 6 : 7-dihydro-derivative failed to absorb hydrogen in acetic acid solution in the presence of Adams catalyst at 20°/760 mm.

The final dehydrogenation step of the synthesis was again carried out by tetrachloro-*o*-benzoquinone. Attempts to dehydrogenate the free base by heating it with palladium–charcoal at 290° gave a product, the light absorption of which ($\lambda_{max.}$ 3200 Å, $\lambda_{min.}$ ~2800 Å) corresponded to that of alstyrine, so that evidently fission of ring C had occurred. A similar attempt using the chloride led to the recovery of part of it unchanged.

The ultraviolet spectra of the synthetic 2 : 3-diethylindolo[2 : 3-*a*]pyridocoline in neutral and alkaline solutions resembled those recorded by Schwyzer [11] for flavocorynanthyrine, and for flavocoryline by Goutarel *et al.*[14] The melting point of the base was 150—151°, while those recorded for flavocorynanthyrine and flavocoryline are 110—112° and 161—162°, respectively. We were, however, able to establish the identity of the perchlorate of the synthetic base with a sample of flavocoryline perchlorate, kindly supplied by Professor Janot, by mixed melting point and infrared spectra.

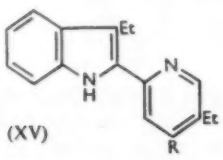
We also synthesised 3-ethyl-2-*iso*propylindolo[2 : 3-*a*]pyridocoline (XI; R = Pr$^i$). The required 2-cyano-5-ethyl-4-*iso*propylpyridine was synthesised from 4-acetyl-5-ethyl-4-methylpyridine by reaction with methylmagnesium iodide, followed by treatment of the resulting tertiary alcohol with hydrogen iodide to give 5-ethyl-2-methyl-4-*iso*propylpyridine. The infrared spectrum of this was almost indistinguishable from that of 4 : 5-diethyl-2-methylpyridine, but a band at 1365 cm.$^{-1}$ in the former was absent in the latter. The base was converted into the nitrile by standard methods, *via* 5-ethyl-4-*iso*propylpyridine-2-carboxylic acid, decarboxylation of which yielded 3-ethyl-4-*iso*propylpyridine, the picrate of which was identical with a sample synthesised by Karrer and Mainoni.[16] The yellow synthetic base (XI; R = Pr$^i$) was initially crystallised from aqueous ethanol and had m. p. 117—118°, softening at 113°. Schwyzer gave m. p. 110—112° for flavocorynanthyrine and it seemed that the synthetic compound might be identical with that of natural origin, although unfortunately it was not possible to obtain a sample of the latter. Later, however we recrystallised our base from methanol and obtained crystals melting at 204°, which, when recrystallised from the same solvent, gave a product of apparently the same composition but of m. p. 149°.

[14] Goutarel, Janot, and Perezamador y Barron, *Bull. Soc. chim. France*, 1954, 863.
[15] Janot and Goutarel, *ibid.*, 1951, 588.
[16] Karrer and Mainoni, *Helv. Chim. Acta*, 1953, **36**, 127.

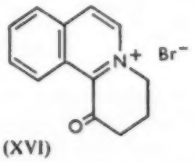
XUM

Bejar, Goutarel, Janot, and Le Hir [17] have deduced structure (XI; R = H) for the alkaloid flavopereirine and we have synthesised a compound of this structure from 2-cyano-5-ethylpyridine. The perchlorate of our base was shown to be identical with a sample of the alkaloid perchlorate, kindly supplied by Professor Janot, by mixed melting point and infrared spectra.

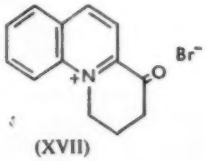
As we had prepared 2-cyano-5-ethyl-4-*iso*propylpyridine, we took the opportunity of synthesising 3-ethyl-2-(5-ethyl-4-*iso*propyl-2-pyridyl)indole (XV; R = Pr$^{i}$), a homologue of alstyrine (XV; R = Et). The melting point of this base (103—104°) is rather close to that of alstyrine (110—111°) and scarcely any depression occurs on mixing them. It is thus possible that the presence of the *iso*propyl compound in the alstyrine obtained by dehydrogenation of alkaloids might escape notice and it should be mentioned that Karrer, Schwyzer, and Flam [18] were able to detect its presence in the dehydrogenation product of demethoxytetrahydrocorynantheine alcohol only by further degradation.



(XV)



(XVI)



(XVII)

Speculation that certain highly potent calabash-curare alkaloids might contain a hexahydrobenzindolopyridocoline nucleus led Boekelheide *et al.* [19,20] to synthesise 5 : 6 : 8 : 9 : 14 : 14a-hexahydrobenz[*e*]indolo[2 : 3-*a*]pyridocoline. However, the methochloride of this base displayed only low curariform activity. We also prepared 5 : 7 : 8 : 13 : 13b : 14-hexahydrobenz[*g*]indolo[2 : 3-*a*]pyridocoline methochloride and Dr. W. D. M. Paton kindly carried out tests on this compound; but it proved to have less than one-tenth of the activity of (+)-tubocurarine. We also attempted to synthesise 8 : 9-dihydro-14*H*-benz[*h*]- and 6 : 7-dihydro-12*H*-benz[*f*]-indolo[2 : 3-*a*]pyridocolinium chloride from 1-cyano*iso*quinoline and 2-cyanoquinoline, respectively, following our general synthetic method. Although we thus succeeded in preparing the bromides (XVI) and (XVII), the phenylhydrazones were recovered unchanged from an attempted Fischer indole reaction.

## Experimental

Ultraviolet absorption measurements were made with a Hilger " Uvispec " spectrophotometer. Those referred to as " alkaline " were made in 0·015N-ethanolic potassium hydroxide and those referred to as " acid " were in ethanolic hydrogen chloride. Difficulty was experienced in obtaining satisfactory analytical results on some of the salts described in this paper, probably owing to solvation. Unless otherwise stated, analytical samples were dried in a vacuum-desiccator at room temperature. M.p.s were measured in open capillaries.

2-*γ*-*Ethoxybutyrylpyridine*.—(*a*) 2-Cyanopyridine (2·5 g.) in ether (50 ml.) was added during 10 min. to an ice-cooled and stirred Grignard reagent, prepared from magnesium (1·2 g.), 1-bromo-3-ethoxypropane [21] (8 g.), and ether (30 ml.). The mixture was then refluxed for 3 hr., cooled in ice, and treated gradually, with stirring, with water (20 ml.) and 5N-sulphuric acid (70 ml.). The ethereal layer was extracted with 2N-sulphuric acid (2 × 70 ml.). The acid extracts were heated on a water-bath for 20 min., cooled, basified with saturated potassium carbonate solution, and extracted with chloroform. Distillation of the dried ($K_2CO_3$) extract gave a colourless liquid (3·2 g.), b. p. 90—98°/0·6 mm., 145°/11 mm., apparently consisting mainly of the *imine* (III), corresponding to the above ketone (Found: C, 68·7; H, 8·55; N, 15·8. $C_{11}H_{15}ON_3$ requires C, 68·75; H, 8·35; N, 14·6%).

[17] Bejar, Goutarel, Janot, and Le Hir, *Compt. rend.*, 1957, **244**, 2066.
[18] Karrer, Schwyzer, and Flam, *Helv. Chim. Acta*, 1952, **35**, 851.
[19] Boekelheide and Ainsworth, *J. Amer. Chem. Soc.*, 1950, **72**, 2134.
[20] Boekelheide and Liu, *ibid.*, 1952, **74**, 4920.
[21] Smith and Sprung, *ibid.*, 1943, **65**, 1276.

(*b*) When the Grignard complex was decomposed by hydrochloric acid (concentrated acid, 15 ml.; water, 15 ml.) and the subsequent heating was omitted, the product (2·25 g.), b. p. 160°/20 mm., again appeared to be mainly the imine, as a strong band was present at 3357 cm.$^{-1}$ (Found: C, 69·25; H, 8·4%).

(*c*) A fresh solution of *n*-butyl-lithium in ether (the double titration method of Gilman and Haubein [22] showed that 1 ml. of this solution was equivalent to 1·44 ml. of N-hydrochloric acid) (8 ml.) was stirred at −50° in nitrogen while 2-bromopyridine (2 g.) in ether was added. After the mixture had been stirred for a further 15 min., a solution of γ-ethoxybutyronitrile [23] (2 g.) in ether was added. After 15 min. at −50°, the mixture was allowed to come to room temperature and stirred for a further 1 hr. Water (15 ml.) and 2N-sulphuric acid (8 ml.) were added and the product (0·75 g.), b. p. 150°/15 mm., was worked up as in (*a*).

Treatment of the above products with warm, ethanolic 2 : 4-dinitrophenylhydrazine containing a few drops of hydrobromic acid yielded the 2 : 4-dinitrophenylhydrazone hydrobromide of the ketone, as orange-yellow needles, m. p. 197°. When this was shaken with chloroform and dilute sodium carbonate solution, the dried ($Na_2SO_4$) chloroform layer yielded the free 2 : 4-*dinitrophenylhydrazone*, which separated from benzene–light petroleum as yellow prisms, m. p. 137° (Found: C, 55·1; H, 5·2. $C_{17}H_{19}O_5N_5$ requires C, 54·70; H, 5·1%).

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxopyridocolinium Bromide* (IV).—The above imine (3 g.) was refluxed for 15 hr. in a current of nitrogen with acetic acid (18 ml.) and constant-boiling hydrobromic acid (9 ml.). The solution was evaporated to dryness (water-bath/reduced pressure) and the residue was dissolved in a small volume of methanol and diluted with acetone. On cooling, the *bromide* (2·75 g.) separated as colourless needles, m. p. 205° (decomp.) (Found: C, 46·2; H, 5·7. $C_9H_{10}ONBr,CH_4O$ requires C, 46·15; H, 5·4%). The corresponding *picrate* separated from ethanol as needles, m. p. 147—148° (Found: C, 47·7; H, 3·2. $C_{15}H_{12}O_8N_4$ requires C, 47·85; H, 3·2%). The 2 : 4-*dinitrophenylhydrazone* of the bromide separated from ethanol as orange-yellow needles, m. p. 192° (decomp.), darkening at 183° (Found: C, 44·95; H, 4·55. $C_{15}H_{14}O_4N_5Br,C_2H_6O$ requires C, 44·9; H, 4·4%), and from acetic acid as pale yellow prisms, m. p. 249—250° (decomp.), becoming red at 220° (Found: C, 42·7; H, 4·3. $C_{15}H_{14}O_4N_5Br,3C_2H_4O_2$ requires C, 42·85; H, 4·4%). With dilute sodium hydroxide solution this yielded a deep blue-violet colour, soluble in chloroform.

The bromide (1·5 g.), phenylhydrazine hydrochloride (0·9 g.), and crystalline sodium acetate (3 g.) were dissolved separately each in a minimum volume of water, mixed, and heated for 3 hr. on a water-bath. On cooling, the resulting solid (2·1 g.) was collected and washed with water; a little more of it was obtained on addition of saturated sodium bromide solution to the filtrate. This *phenylhydrazone* of the bromide separated from ethanol–ether as orange-brown prisms, m. p. 271° (decomp.) (for analysis dried for 24 hr. at 105°/1 mm.) (Found: C, 55·1; H, 5·2. $C_{15}H_{16}N_3Br,0{\cdot}5H_2O$ requires C, 55·05; H, 5·2%). The corresponding *phenylhydrazone picrate* separated from dimethylformamide–ethanol as orange-red crystals, m. p. 225° (decomp.) (Found: C, 54·7; H, 3·95. $C_{21}H_{18}O_7N_6$ requires C, 54·1; H, 3·9%).

6 : 7-*Dihydro*-12H-*indolo*[2 : 3-a]*pyridocolinium Chloride* (V; R = H, X = Cl).—A solution of the phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide (1·5 g.) in absolute ethanol (45 ml.) was cooled in ice, saturated with dry hydrogen chloride, kept at room temperature for 1 hr., and then refluxed for 5 hr. The mixture was kept overnight at 0° and the product was collected, washed with ice-cold ethanol, and recrystallised from methanol–ethanol, giving the *chloride* (1·2 g.) as bright yellow needles, m. p. 340° (decomp.) (Found: C, 65·2; H, 5·8. $C_{15}H_{13}N_2Cl,H_2O$ requires C, 65·55; H, 5·45%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2170, 2520, 3140, and 3850 Å (log ε 4·35, 3·93, 4·15, and 4·16), $\lambda_{min.}$ 2390, 2745, and 3410 Å (log ε 3·83, 3·42, and 3·89); (*b*) alkaline, $\lambda_{max.}$ 2230, 2645, 3630, and 4200 Å (log ε 4·37, 4·04, 4·09, and 4·19), $\lambda_{min.}$ 2490, 2940, and 3780 Å (log ε 3·87, 3·55, and 4·06).

The corresponding *picrate* separated from dimethylformamide–methanol as needles, m. p. 249° (decomp.) (Found: C, 55·9; H, 3·45. $C_{21}H_{15}O_7N_5$ requires C, 56·1; H, 3·35%). Addition of saturated sodium nitrate solution to an aqueous solution of the chloride precipitated the *nitrate*, which separated from ethanol as orange-yellow needles, m. p. 259° (decomp.) (Found: C, 63·65; H, 4·8. $C_{15}H_{13}O_2N_3$ requires C, 63·6; H, 4·6%).

2-2′-*Pyridylindole Methiodide* (VIII; R = Me, X = I).—2-Acetylpyridine phenylhydrazone was recovered unchanged after an attempt to effect a Fischer indole reaction in refluxing

[22] Gilman and Haubein, *J. Amer. Chem. Soc.*, 1944, **66**, 1515.
[23] Wertheim, *ibid.*, 1934, **56**, 735.

ethanolic hydrogen chloride. However, the reaction succeeded by the use of polyphosphoric acid, as described by Sugasawa, Terashima, and Kanaoka.[24] The resulting 2-2′-pyridylindole was largely unchanged when refluxed for 7 hr. with excess of methyl iodide, and the *methiodide* was therefore prepared by 20 hours' heating at 100°. It was isolated by dilution with ether and separated from methanol as yellow needles, m. p. 238° (Found: C, 47·4; H, 4·2. $C_{14}H_{13}N_2I,H_2O$ requires C, 47·45; H, 4·25%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2180, 2520, and 3730 Å (log ε 4·53, 3·93, and 4·25), $\lambda_{min.}$ 2450 and 2750 Å (log ε 3·93 and 3·51); (*b*) alkaline, $\lambda_{max.}$ 2200, 2640, and 4150 Å (log ε 4·56, 4·03, and 4·31), $\lambda_{min.}$ 2470 and 2900 Å (log ε 3·80 and 3·32). Light absorption of 2-2′-pyridylindole: (*a*) acid, $\lambda_{max.}$ 2170, 2510, 3090, and 3760 Å (log ε 4·21, 3·94, 4·09, and 4·27), $\lambda_{min.}$ 2350, 2730, and 3290 Å (log ε 3·86, 3·57, and 4·00); (*b*) neutral, $\lambda_{max.}$ 2200, 2290, and 3250 Å (log ε 4·22, 4·21, and 4·42), $\lambda_{min.}$ 2250 and 2710 Å (log ε 4·19 and 3·52). Light absorption of 2-(4 : 5-diethyl-2-pyridyl)-3-ethylindole: (*a*) acid, $\lambda_{max.}$ 2230 and 3710 Å (log ε 4·53 and 4·19), $\lambda_{min.}$ 2750 Å (log ε 3·55); (*b*) neutral, $\lambda_{max.}$ 3250 Å (log ε 4·39), $\lambda_{min.}$ 2740 Å (log ε 3·71). Light absorption of 2-4′-pyridylindole: (*a*) acid, $\lambda_{max.}$ 2170, 2530, and 3850 Å (log ε 4·06, 4·02, and 4·44), $\lambda_{min.}$ 2340 and 2830 Å (log ε 3·82 and 3·21); (*b*) neutral, $\lambda_{max.}$ 2240, 2450, and 3300 Å (log ε 4·17, 4·11, and 4·38), $\lambda_{min.}$ 2350 and 2690 Å (log ε 4·06 and 3·37). Light absorption of 2-4′-pyridylindole methiodide: (*a*) acid, $\lambda_{max.}$ 2200, 2550, 3800, and 3900 Å (log ε 4·34, 4·02, 4·44, and 4·44), $\lambda_{min.}$ 2500, 2900, and 3840 Å (log ε 3·93, 3·26, and 4·42); (*b*) alkaline, $\lambda_{max.}$ 2220, 2500, and 4300 Å (log ε 4·40, 4·02, and 4·43), $\lambda_{min.}$ 2450 and 3020 Å (log ε 4·00 and 3·33).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*Octahydro*-12H-*indolo*[2 : 3-a]*pyridocoline* (VI).—The above chloride (V; R = H, X = Cl) (80·6 mg.) in acetic acid (10 ml.) absorbed 20·5 ml. of hydrogen at 18°/760 mm. during 4 hr. in the presence of freshly reduced Adams catalyst. Towards the end of the hydrogenation the sparingly soluble colourless hydrochloride of the product separated and the yellow colour of the solution disappeared. Before filtration, the solution was heated to dissolve this salt, and the filtrate was evaporated to dryness (water-bath; reduced pressure). The residue was recrystallised twice from ethanol, giving the hydrochloride, m. p. 302° (decomp.). An aqueous solution of this was basified with sodium hydroxide; the resulting base (VI) separated from light petroleum (b. p. 60—80°) as colourless prisms, m. p. 150° (Found: C, 79·55; H, 8·3. Calc. for $C_{15}H_{18}N_2$: C, 79·65; H, 8·0%). When mixed with a sample (m. p. 147—148°) synthesised by Groves and Swan,[7] it had m. p. 149°.

6 : 7-*Dihydro*-12-*methylindolo*-12H-[2 : 3-a]*pyridocolinium Iodide* (V; R = Me, X = I).—(*a*) 1 : 2 : 3 : 4-Tetrahydro-1-oxopyridocolinium bromide (0·25 g.) was treated with 1-methyl-1-phenylhydrazine (0·17 g.) in the presence of N-hydrochloric acid (1·5 ml.) and crystalline sodium acetate (0·75 g.) as described above for the corresponding phenylhydrazone. The resulting 1 : 2 : 3 : 4-*tetrahydro*-1-*oxopyridocolinium* 1-*methyl*-1-*phenylhydrazone* was, however, isolated as the *iodide* (0·37 g.), the bromide being too soluble in water, by addition of saturated potassium iodide solution to the reaction mixture. This separated from ethanol as orange needles, m. p. 203° (for analysis dried for 2·5 hr. at 95°/0·5 mm.) (Found: C, 50·5; H, 4·85. $C_{16}H_{18}N_3I$ requires C, 50·65; H, 4·75%). This was subjected to a Fischer indole reaction, as above, and the resulting solution was concentrated to one-third of its volume and kept at 0°; then ammonium chloride and a small amount of brown solid were removed by filtration. The filtrate was evaporated to dryness (water-bath; reduced pressure), the residue was dissolved in water, and the solution filtered and treated with saturated potassium iodide solution. The precipitated *iodide* (V; R = Me, X = I) was collected, washed with water, and recrystallised from methanol, affording deep yellow needles, m. p. 295° (decomp.) (Found: C, 50·45; H, 4·4. $C_{16}H_{15}N_3I,H_2O$ requires C, 50·55; H, 4·45%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2120, 2510, 3150, and 3780 Å (log ε 4·60, 4·07, 4·10, and 4·21), $\lambda_{min.}$ 2400, 2760, and 3370 Å (log ε 3·99, 3·38, and 3·95); (*b*) alkaline, $\lambda_{max.}$ 2530, 3150, and 3770 Å (log ε 4·06, 4·09, and 4·19), $\lambda_{min.}$ 2400, 2750, and 3380 Å (log ε 3·97, 3·34, and 3·92).

(*b*) A solution of 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium chloride in a small volume of water was treated with 40% sodium hydroxide solution; a bright red precipitate was collected, washed with a little cold water, and dried for 2 days in a vacuum-desiccator. It was then mixed with excess of methyl iodide, kept overnight at room temperature, then refluxed for 1 hr. The residue left on evaporation was recrystallised twice from methanol, affording the *iodide* (V; R = Me, X = I) as deep yellow needles, m. p. 292° (decomp.); when mixed with a specimen prepared according to (*a*) it had m. p. 295° (decomp.).

[24] Sugasawa, Terashima, and Kanaoka, *Pharm. Bull.* (*Japan*), 1956, **4**, 16.

*Dehydrogenation of* 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*Octahydro*-12H-*indolo*[2 : 3-a]*pyridocoline*.—The temperature of a mixture of the base (VI) (50 mg.) and acidic palladium–charcoal [11] (100 mg.) was gradually raised to 260° during 20 min. Hydrogen evolution began at 200° and ceased at 260°. After cooling, the mixture was extracted with methanol. The residue left on evaporation of the extract was dissolved in warm, dilute hydrochloric acid, and the solution was basified with aqueous ammonia, and extracted with ether. The solvent was removed from the dried ($K_2CO_3$) extract, leaving an oil which rapidly crystallised, giving 1-*butyl*-β-*carboline* (XII), which separated from benzene–light petroleum (charcoal) as cream-coloured prisms (20 mg.), m. p. 166° Found: C, 79·75; H, 7·25. $C_{15}H_{16}N_2$ requires C, 80·35; H, 7·15%). Light absorption in EtOH: $\lambda_{max.}$ 2350, 2900, 3340, and 3500 Å (log ε 4·61, 4·24, 3·73, and 3·75), $\lambda_{min.}$ 2680, 3000, and 3450 Å (log ε 3·73, 3·10, and 3·68).

12H-*Indolo*[2 : 3-a]*pyridocolinium Chloride* (II; R = H, X = Cl).—The 6 : 7-dihydro-compound (V; R = H, X = Cl) (80 mg.) in ethanol (10 ml.) was refluxed for 15 hr. with tetrachloro-*o*-benzoquinone (0·4 g.), the solvent was removed, and the residue crystallised from methanol–ether, giving the *chloride* (35 mg.) as pale yellow needles, decomp. 295° (Found: C, 65·6; H, 4·9. $C_{15}H_{11}N_2Cl,H_2O$ requires C, 66·05; H, 4·8%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2440, 2940, 3450, and 3880 Å (log ε 4·43, 4·12, 4·27, and 4·10), $\lambda_{min.}$ 2680, 3050, and 3770 Å (log ε 3·96, 4·03, and 4·05); (*b*) alkaline, $\lambda_{max.}$ 2270, 2410, 2890, 3200, 3490, 3700, and 4490 Å (log ε 4·42, 4·32, 4·43, 4·09, 4·26, 4·22, and 3·63), $\lambda_{min.}$ 2370, 2620, 3100, 3280, 3600, and 4180 Å (log ε 4·30, 4·13, 4·02, 4·05, 4·19, and 3·57). The corresponding picrate separated from dimethylformamide–ethanol as needles, m. p. 252—253° (decomp.).

12-*Methylindolo*-12H-[2 : 3-a]*pyridocolinium Iodide* (XIII).—This *iodide* was prepared from the above chloride in essentially the manner described under (*b*) for 6 : 7-dihydro-12-methyl-12*H*-indolo[2 : 3-*a*]pyridocolinium iodide and, after being recrystallised four times from methanol, formed yellow crystals, m. p. 360° (decomp.) (Found: C, 53·6; H, 3·9. $C_{16}H_{13}N_2I$ requires C, 53·35; H, 3·6%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2240, 2480, 2930, 3360, and 3990 Å (log ε, 4·52, 4·31, 4·08, 4·27, and 4·07), $\lambda_{min.}$ 2450, 2830, 3050, and 3760 Å (log ε 4·30, 4·01, 3·98, and 3·96); (*b*) alkaline, $\lambda_{max.}$ 2250, 2530, 3300, and 4000 Å (log ε 4·51, 4·33, 4·27, and 4·08), $\lambda_{min.}$ 2460, 2830, and 3780 Å (log ε 4·30, 4·05, and 4·00).

2-*Cyano*-4 : 5-*diethylpyridine*.—This was prepared by Lee and Swan's [25] route; but modifications led to the yields of many stages being improved. In the formation of the *N*-oxide of 5-ethyl-2-methylpyridine, increasing the time of heating to 26 hr. afforded a yield of 89·5% and on a 227 g. scale this was nitrated in 72% yield. The nitro-compound (60 g.) in benzene (300 ml.) when refluxed with phosphorus tribromide (250 ml.) for 12 hr. afforded 4-bromo-5-ethyl-2-methylpyridine in 72% yield. This, when heated with cyanide for only 12 hr. at 180—200° in the autoclave yielded ethyl 5-ethyl-2-methylpyridine-4-carboxylate in 79% yield. Clemmensen reduction of 36·5 g. of 4-acetyl-5-ethyl-2-methypyridine (12 hours' reflux) and treatment of the alcoholic by-product with hydriodic acid afforded 4 : 5-diethyl-2-methypyridine in almost theoretical yield. Oxidation of the styryl compound (16 g.), followed by esterification of the crude product, after removal of benzoic acid, afforded ethyl 4 : 5-diethylpyridine-2-carboxylate in 56·5% yield. The corresponding amide (7·7 g.) was converted into 2-cyano-4 : 5-diethylpyridine in 69·5% yield.

2-γ-*Ethoxybutyryl*-4 : 5-*diethylpyridine*.—When 2-cyano-4 : 5-diethylpyridine (3 g.) was treated with a Grignard reagent prepared from magnesium (1·5 g.) and 1-bromo-3-ethoxypropane (10 g.) as described under (*a*) for 2-γ-ethoxybutyrylpyridine; the product (2·8 g.), b. p. 132—140°/0·2 mm., had a strong absorption band at 3354 cm.$^{-1}$ and appeared to be the *imine* corresponding to this ketone (Found: C, 72·7; H, 9·95; N, 10·8. $C_{15}H_{24}ON_2$ requires C, 72·75; H, 9·7; N, 11·3%). The 2 : 4-*dinitrophenylhydrazone* of 2-γ-ethoxybutyryl-4 : 5-diethylpyridine hydrobromide separated from ethanol as yellow needles, m. p. 202° (decomp.) (Found: C, 49·2; H, 5·85. $C_{21}H_{27}O_5N_5,HBr$ requires C, 49·4; H, 5·5%). The corresponding *base*, recrystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 109—110° (Found: C, 58·85; H, 6·6. $C_{21}H_{27}O_5N_5$ requires C, 55·75; H, 6·3%).

*Action of Hydrobromic Acid on* 2-γ-*Ethoxybutyrimidoyl*-4 : 5-*diethylpyridine*.—The product obtained by refluxing the above imine (1 g.) with acetic–hydrobromic acid for 21 hr., as for the preparation of 1 : 2 : 3 : 4-tetrahydro-1-oxopyridocolinium bromide, failed to crystallise. It was dissolved in a small volume of water, basified with sodium carbonate, and extracted with chloroform, as it was thought that perhaps cyclisation had not occurred. However, evaporation

[25] Lee and Swan, *J.*, 1956, 771.

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of the dried ($Na_2SO_4$) extract yielded only an oil (0·8 g.), but this was converted into the 7 : 8-*diethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*phenylhydrazonopyridocolinium bromide* (0·5 g.), separating from ethanol–ether as yellow cubes, m. p. 255° (Found: C, 60·75; H, 6·7. $C_{19}H_{24}N_3Br$ requires C, 60·95; H, 6·4%). On two occasions, when the imine was treated with hydrobromic acid, a small amount of 2-*γ-bromobutyryl*-4 : 5-*diethylpyridine hydrobromide* was isolated; it separated from methanol–acetone as colourless plates, m. p. 155—156° (Found: C, 43·1; H, 5·7. $C_{13}H_{18}ONBr,HBr$ requires C, 42·75; H, 5·2%). Basification of this salt yielded an oil.

2 : 3-*Diethyl*-6 : 7-*dihydro*-12H-*indolo*[2 : 3-a]*pyridocolinium Chloride*.—This *chloride* (35 mg.) was obtained from the above phenylhydrazone bromide (55 mg.) by the Fischer indole reaction, as before and separated from ethanol as bright yellow needles, decomposing at 273° (Found: C, 67·05; H, 7·2. $C_{19}H_{21}N_2Cl,1·5H_2O$ requires C, 67·15; H, 7·05%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2220, 3120, and 3880 Å (log ε 4·41, 4·19, and 4·20), $\lambda_{min.}$ 2760, and 3390 Å (log ε 3·51 and 3·94); (*b*) alkaline, $\lambda_{max.}$ 2300, 2630, 3610, and 4110 Å (log ε 4·44, 4·01, 4·13, and 4·23), $\lambda_{min.}$ 2520, 2920, and 3740 Å (log ε 3·95, 3·50, and 4·12). The corresponding *picrate* separated from ethanol–acetone as needles, decomp. 253° (Found: C, 59·15; H, 4·65. $C_{25}H_{23}O_7N_5$ requires C, 59·4; H, 4·55%). The corresponding *nitrate* separated from ethanol as yellow needles, m. p. 262—263° (Found: C, 68·05; H, 7·1. $C_{19}H_{21}O_3N_3$ requires C, 67·25; H, 6·2%).

2 : 3-*Diethyl*-12H-*indolo*[2 : 3-a]*pyridocolinium Chloride*.—Dehydrogenation of the above 6 : 7-dihydro-chloride with tetrachloro-*o*-benzoquinone, as before, yielded the pale yellow *chloride*, which crystallised from ethanol–ether and decomposed at 258° (Found: C, 67·8; H, 6·3. $C_{19}H_{19}N_2Cl,1·5H_2O$ requires C, 67·55; H, 6·5%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2380, 2910, 3460, and 3850 Å (log ε 4·52, 4·15, 4·30, and 4·24), $\lambda_{min.}$ 2750, 3050, and 3740 Å (log ε 4·04, 4·05, and 4·16); (*b*) alkaline, $\lambda_{max.}$ 2310, 2410, 2880, 3180, 3640, and 4400 Å (log ε 4·43, 4·42, 4·44, 4·07, 4·31, and 3·74), $\lambda_{min.}$ 2370, 2650, 3090, 3260, and 4190 Å (log ε 4·41, 4·14, 4·03, 4·05, and 3·72). Basification of an aqueous solution of the chloride yielded 2 : 3-*diethylindolo*[2 : 3-a]-*pyridocoline*, which was purified by chromatography in chloroform on alumina and then separated from methanol as deep yellow needles, m. p. 150—151° (Found: C, 75·25; H, 7·25. $C_{19}H_{18}N_2,1·5H_2O$ requires C, 75·55; H, 7·0%). This base, in methanol solution, yielded a perchlorate as pale yellow needles, m. p. 301° (decomp.). The sample of flavocoryline perchlorate supplied by Professor Janot, under the same conditions, had m. p. and mixed m. p. 304° (decomp.).

5-*Ethyl*-2-*methyl*-4-iso*propylpyridine*.—A solution of 4-acetyl-5-ethyl-2-methylpyridine (10·8 g.) in ether (100 ml.) was added during 10 min. with stirring at room temperature to a Grignard reagent, prepared from magnesium (4·1 g.), methyl iodide (24·3 g.), and ether (125 ml.), and the mixture was stirred and refluxed for 3 hr., then cooled in ice, decomposed by saturated ammonium chloride solution (210 ml.) and concentrated hydrochloric acid (35 ml.), basified with 10% aqueous sodium hydroxide, and extracted with chloroform. The crude tertiary alcohol (11·8 g.), a very viscous, pale yellow liquid, obtained by evaporation of the solvent from the dried ($Na_2SO_4$) extract, was refluxed with freshly distilled constant-boiling hydriodic acid (86 ml.) and red phosphorus (4·5 g.) for 6 hr. The mixture was diluted with water, filtered, basified with 20% aqueous sodium hydroxide, and extracted with chloroform. Distillation of the dried ($Na_2SO_4$) extract gave the *base* (9·2 g., 85%), b. p. 105—106°/20 mm. (Found: C, 80·7; H, 10·55. $C_{11}H_{17}N$ requires C, 81·0; H, 10·4%). The *picrate* separated from ethanol as prisms, m. p. 179—180° (Found: C, 51·8; H, 5·2. $C_{11}H_{17}N,C_6H_3O_7N_3$ requires C, 52·05; H, 5·1%).

5-*Ethyl*-4-iso*propyl*-2-*styrylpyridine*.—When the above base (10·5 g.) was condensed with benzaldehyde as described [25] for 4 : 5-diethyl-2-methylpyridine except that the mixture was refluxed for 96 hr., the *product* (10·5 g.) was obtained as a pale yellow liquid, b. p. 188—194°/2 mm. (Found: C, 86·15; H, 8·8. $C_{18}H_{21}N$ requires C, 86·05; H, 8·35%), together with unchanged base (3 g.). The *picrate* separated from dimethylformamide–ethanol as needles, m. p. 235—236° (decomp.), softening at 213° (Found: C, 60·25; H, 5·25. $C_{18}H_{21}N,C_6H_3O_7N_3$ requires C, 60·0; H, 5·0%).

*Ethyl* 5-*Ethyl*-4-iso*propylpyridine*-2-*carboxylate*.—The above styryl compound (10·5 g.) was oxidised as described [25] for 4 : 5-diethyl-2-styrylpyridine, except that, after removal of the benzoic acid, the solution was evaporated to dryness (water-bath/reduced pressure). The residue was treated with absolute ethanol, which was then evaporated, and the residue was again mixed with ethanol (150 ml.), saturated with hydrogen chloride at 0°, kept at room temperature overnight, and refluxed for 4 hr. The mixture was evaporated to dryness (water-bath/reduced pressure), the residue was cooled, diluted with water, basified with saturated aqueous sodium

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carbonate, and extracted with chloroform. Distillation of the dried ($K_2CO_3$) extract gave the *ester* (5·2 g.), b. p. 125—129°/0·5 mm. (Found: C, 70·85; H, 8·9. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6%). The *picrate* separated from ethanol as prisms, m. p. 111°, softening at 106° (Found: C, 50·45; H, 5·3. $C_{13}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 50·75; H, 5·3%).

*5-Ethyl-4-isopropylpyridine-2-carboxylic Acid.*—The ester (0·45 g.) was refluxed with ethanol (10 ml.) and 40% aqueous potassium hydroxide solution (2·5 ml.) for 5 hr., the ethanol was removed, and the residue was extracted with ether. The solution was then adjusted to pH 4 and extracted continuously with ether for 30 hr. The *acid* left on evaporation of the latter, dried ($Na_2SO_4$) extract separated from methanol–ether as colourless crystals (0·23 g.), m. p. 147°, unchanged by sublimation at 60—80°/0·01 mm. (Found: C, 68·65; H, 8·25. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·75%). In air this absorbed moisture (Found: C, 63·0; H, 8·1. $C_{11}H_{15}O_2N,H_2O$ requires C, 62·55; H, 8·05%). Light absorption in EtOH: $\lambda_{max.}$ 2670 and 2340 Å (log ε 3·64 and 3·78), $\lambda_{min.}$ 2525 Å (log ε 3·48).

When heated with copper powder the acid yielded a distillate which gave a picrate, separating from ethanol as needles, m. p. 136—137°, softening at 123°, not depressed on admixture with 3-ethyl-4-*iso*propylpyridine picrate supplied by Professor Karrer (Found: C, 50·6; H, 4·75. Calc. for $C_{10}H_{15}N,C_6H_3O_7N_3$: C, 50·8; H, 4·75%).

*2-Carbamoyl-5-ethyl-4-isopropylpyridine.*—The above ester (4·9 g.) when shaken for 72 hr. with aqueous ammonia (*d* 0·88; 49 ml.) yielded the *amide* (3·8 g.) which, when sublimed at 60—80°/0·01 mm., had m. p. 164—165° (Found: C, 68·75; H, 8·7. $C_{11}H_{16}ON_2$ requires C, 68·75; H, 8·3%).

*2-Cyano-5-ethyl-4-isopropylpyridine.*—Dehydration of the amide (3·8 g.) in the way described [25] for the 4 : 5-diethyl compound, but with a reaction time of 3·5 hr., gave the *cyanopyridine* (2·75 g.), b. p. 113—117°/0·2 mm. (Found: C, 75·45; H, 8·2; N, 15·5. $C_{11}H_{14}N_2$ requires C, 75·85; H, 8·05; N, 16·1%).

*2-γ-Ethoxybutyryl-5-ethyl-4-isopropylpyridine.*—Treatment of the preceding nitrile with 3-ethoxypropylmagnesium bromide as described under (*a*) for 2-γ-ethoxybutyrylpyridine gave the ketone, b. p. 165°/2 mm. (Found: C, 72·85; H, 10·35; N, 6·0. $C_{16}H_{25}O_2N$ requires C, 73·0; H, 9·5; N, 5·3%). The 2 : 4-*dinitrophenylhydrazone* separated from light petroleum (b. p. 60—80°) as orange plates, m. p. 94° (Found: C, 59·6; H, 6·8. $C_{22}H_{29}O_5N_5$ requires C, 59·6; H, 6·55%).

*Action of Hydrobromic Acid on 2-γ-Ethoxybutyryl-5-ethyl-4-isopropylpyridine.*—When the above ketone (1·15 g.) was treated with hydrobromic acid as before, the residue left on evaporation of the solution yielded colourless crystals (0·34 g.), m. p. 145—147° (from methanol–acetone). Recrystallisation from the same solvent gave colourless plates, m. p. 150—151°, of *2-γ-bromobutyryl-5-ethyl-4-isopropylpyridine hydrobromide* (for analysis dried for 4 hr. at 50°/0·1 mm.) (Found: C, 44·4; H, 5·75. $C_{14}H_{21}ONBr_2$ requires C, 44·35; H, 5·55%). An aqueous solution of this salt was basified with sodium carbonate and extracted with ether and the dried ($K_2CO_3$) extract yielded a gum. This readily afforded *7-ethyl-1 : 2 : 3 : 4-tetrahydro-1-phenylhydrazono-8-isopropylpyridocolinium bromide*, which separated from ethanol–ether as yellow crystals, m. p. 256—257°, although melting at a much lower temperature if heated rapidly, apparently owing to hydration (Found: C, 59·85; H, 7·1. $C_{20}H_{26}N_3Br,0·5H_2O$ requires C, 60·5; H, 6·8%). A further quantity of this compound was obtained by the action of phenylhydrazine on the residue left on evaporation of the methanol–acetone mother-liquor from which the 2-γ-bromobutyryl-5-ethyl-4-*iso*propylpyridine hydrobromide had been obtained.

*3-Ethyl-6 : 7-dihydro-2-isopropyl-12H-indolo[2 : 3-a]pyridocolinium Chloride.*—This *salt*, obtained by the Fischer indole reaction on the above phenylhydrazone, separated from ethanol–ether as bright yellow crystals, decomp. 260° (Found: C, 72·05; H, 7·35. $C_{20}H_{23}N_2Cl,0·5H_2O$ requires C, 71·55; H, 7·15%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2220, 3140, and 3880 Å (log ε 4·44, 4·25, and 4·22), $\lambda_{min.}$ 2750 and 3410 Å (log ε 3·58, 3·97); (*b*) alkaline, $\lambda_{max.}$ 2310, 2660, 3600, and 4110 Å (log ε 4·45, 4·04, 4·16, and 4·23), $\lambda_{min.}$ 2520, 2910, and 3770 Å (log ε 3·95, 3·41, and 4·13).

*3-Ethyl-2-isopropyl-12H-indolo[2 : 3-a]pyridocolinium Chloride.*—(*a*) Dehydrogenation of the above 6 : 7-dihydro-chloride with tetrachloro-*o*-benzoquinone, as before, yielded the pale yellow *chloride* which, when crystallised from ethanol–ether, decomposed at 270° (Found: C, 70·6; H, 6·3. $C_{20}H_{21}N_2Cl,H_2O$ requires C, 70·05; H, 6·7%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2400, 2920, 3460, and 3860 Å (log ε 4·55, 4·15, 4·29, and 4·25), $\lambda_{min.}$ 2760, 3050, and 3750 Å (log ε 3·99, 4·02, and 4·16); (*b*) alkaline, $\lambda_{max.}$ 2310, 2890, 3180, 3610, and 4420 Å (log ε 4·43, 4·43, 4·07, 4·30, and

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3·71), $\lambda_{min.}$ 2620, 3090, 3280, and 4180 Å (log ε 4·12, 4·01, 4·03, and 3·67). Basification of an aqueous solution of this chloride yielded 3-*ethyl*-2-iso*propylindolo*[2 : 3-a]*pyridocoline* (XI; R = Pr$^i$) which, when recrystallised from dilute ethanol, had m. p. 117—119° after softening at 113° (Found: C, 76·15; H, 7·55. $C_{20}H_{21}N_2Cl,H_2O$ requires C, 76·2; H, 7·3%).

(*b*) The 6 : 7-dihydro-chloride (0·2 g.) and tetrachloro-*o*-benzoquinone (0·35 g.) were heated together in acetic acid (2·5 ml.) for 8 hr. on a water-bath. The mixture was cooled and diluted with ether, and the solid was collected, washed with ether, and shaken with chloroform and sodium hydroxide solution until it passed into solution. The chloroform extract was dried ($K_2CO_3$), the solvent removed, the residue was dissolved in ethanol containing a little hydrochloric acid, and ether added to the solution. The resulting precipitate was dissolved in water and basified with ammonia. The resulting bright yellow solid was chromatographed in chloroform on alumina. The product formed deep yellow crystals (50 mg.; m. p. 204°) from methanol; but when recrystallised from the same solvent, the *base* had m. p. 149° (Found: C, 77·5; H, 7·1. $C_{20}H_{20}N_2,1·25H_2O$ requires C, 77·55; H, 6·95%). The *perchlorate* formed pale yellow needles, m. p. 312° (decomp.), from methanol (Found: C, 61·55; H, 5·75. $C_{20}H_{21}O_4N_2Cl$ requires C, 61·75; H, 5·4%).

2-γ-*Ethoxybutyryl*-5-*ethylpyridine*.—2-Cyano-5-ethylpyridine [25] (1·77 g.) when treated with 3-ethoxypropylmagnesium bromide as under (*b*) for 2-γ-ethoxybutyrylpyridine gave the *ketone* (1·77 g.), b. p. 150—160°/3 mm. (Found: C, 70·1; H, 9·3. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6%). Only a trace of an absorption band in the 3360 cm.$^{-1}$ region was present.

7-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*oxopyridocolinium Bromide*.—When the above ketone (1·65 g.) was treated with hydrobromic acid in the usual way, the resulting pyridocolinium bromide failed to crystallise and was therefore converted directly into the *phenylhydrazone* which, when recrystallised from ethanol–ether, weighed 1·22 g. and had m. p. 279°.

3-*Ethyl*-6 : 7-*dihydro*-12H-*indolo*[2 : 3-a]*pyridocolinium Nitrate*.—The above phenylhydrazone (0·5 g.) in a Fischer indole reaction yielded the chloride (0·33 g.), which was converted into the *nitrate*, separating from ethanol as yellow needles, m. p. 267° (decomp.) (Found: C, 65·25; H, 5·4. $C_{17}H_{17}O_3N_3$ requires C, 65·6; H, 5·45%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2130, 2520, 3160, and 3950 Å (log ε 4·41, 3·95, 4·21, and 4·16), $\lambda_{min.}$ 2430, 2750, and 3450 Å (log ε 3·88, 3·55, and 3·92); (*b*) alkaline, $\lambda_{max.}$ 2220, 2670, 3600, and 4230 Å (log ε 4·40, 4·01, 4·09, and 4·21), $\lambda_{min.}$ 2490, 2950, and 3830 Å (log ε 3·83, 3·32, and 4·05).

3-*Ethyl*-12H-*indolo*[2 : 3-a]*pyridocolinium Perchlorate*.—The above 6 : 7-dihydro-chloride (0·13 g.) was heated with tetrachloro-*o*-benzoquinone (0·23 g.) in acetic acid (2 ml.) for 9 hr. on a water-bath and worked up as under (*b*) for the 3-ethyl-2-*iso*propyl compound, except that the dehydrogenated chloride was dissolved in methanol and treated with perchloric acid. The resulting *perchlorate* separated from methanol as pale yellow needles (38 mg.), m. p. 331° (decomp.) (Found: C, 56·7; H, 5·05. $C_{17}H_{15}O_4N_2Cl,CH_4O$ requires C, 57·05; H, 5·0%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2350, 2950, 3500, and 3900 Å (log ε 4·52, 4·21, 4·32, and 4·20), $\lambda_{min.}$ 2730, 3090, and 3820 Å (log ε 4·03, 4·07, and 4·16); (*b*) alkaline, $\lambda_{max.}$ 2300, 2350, 2890, 3200, 3660, and 4500 Å (log ε 4·46, 4·45, 4·49, 4·10, 4·33, and 3·68), $\lambda_{min.}$ 2320, 2670, 3100, 3300, and 4200 Å (log ε 4·44, 4·14, 4·08, 4·05, and 3·62). The sample of flavopereirine perchlorate supplied by Professor Janot melted at 330° (decomp.) under the same conditions, and had mixed m. p. 330° (decomp.).

2-*Butyryl*-5-*ethyl*-4-iso*propylpyridine*.—2-Cyano-5-ethyl-4-*iso*propylpyridine (0·81 g.) when treated with *n*-propylmagnesium bromide as described for the preparation of 2-butyryl-4 : 5-diethylpyridine [25] gave the *ketone* (0·3 g.), b. p. 80—90°/1 mm. (Found: C, 76·6; H, 9·95. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·6%).

3-*Ethyl*-2-(5-*ethyl*-4-iso*propyl*-2-*pyridyl*)*indole* (XV; R = Pr$^i$).—When the preceding ketone (0·3 g.) was subjected to a Fischer indole reaction as for the synthesis of 2-(4 : 5-diethyl-2-pyridyl)-3-ethylindole [25] it yielded the *base*, b. p. 184—195°/0·3 mm. (bath-temp.), which solidified on trituration with light petroleum and recrystallised first from methanol, then from light petroleum (b. p. 40—60°), as colourless prisms, m. p. 103—104° (Found: C, 82·3; H, 8·65. $C_{20}H_{24}N_2$ requires C, 82·2; H, 8·2%). The yellow *hydrochloride*, crystallised from methanol–ethyl acetate, softened at 190°, and had m. p. 221—223° (decomp.) (Found: C, 71·6; H, 7·8. $C_{20}H_{25}N_2Cl,0·5H_2O$ requires C, 71·1; H, 7·7%). Light absorption in EtOH: $\lambda_{max.}$ 3260 Å (log ε 4·30), $\lambda_{min.}$ 2730 Å (log ε 3·61). The *picrate* separated from dimethylformamide–ethanol as needles, m. p. 211—213° (decomp.) (Found: C, 59·35; H, 5·15. $C_{20}H_{24}N_2,C_6H_3O_7N_3,0·5C_2H_6O$ requires C, 59·55; H, 5·5%).

*4-Chloro-5-ethyl-2-methylpyridine 1-Oxide.*—Acetyl chloride (5 ml.) was added to 5-ethyl-2-methyl-4-nitropyridine 1-oxide [25] (2 g.) with ice-cooling and after 1 hr. at room temperature the mixture was heated for 2 hr. at 55—60°, cooled in ice, treated with water, basified with sodium carbonate, and extracted with ether. The dried ($K_2CO_3$) extract on distillation yielded the *product* (1·5 g.), b. p. 140°/3 mm., which crystallised (Found: C, 55·8; H, 6·15. $C_8H_{10}ONCl$ requires C, 56·0; H, 5·85%). This was recovered unchanged after being refluxed for 48 hr. with aqueous-ethanolic potassium cyanide containing a little potassium iodide. The action of acetyl bromide on 5-ethyl-2-methyl-4-nitropyridine 1-oxide gave a product which became tarry on distillation. When the last-named compound (1 g.) was refluxed for 4 hr. with 48% hydrobromic acid (4 ml.), and the resulting solution kept at room temperature, dark red crystals (0·87 g.) separated. These were recrystallised from benzene, giving orange-yellow plates, m. p. 118—119° (Found: C, 32·05; H, 3·6. $2C_8H_{10}O_2N_2,Br_2$ requires C, 31·8; H, 3·3%). Treatment of the latter, in chloroform solution, with aqueous sodium carbonate gave back 5-ethyl-2-methyl-4-nitropyridine 1-oxide, m. p. 80° (Found: C, 52·85; H, 5·5. Calc. for $C_8H_{10}O_2N_2$: C, 52·75; H, 5·5%).

*5 : 7 : 8 : 13 : 13b : 14-Hexahydrobenz[g]indolo[2 : 3-a]pyridocoline Methiodide.*—A solution of the base [Swan,[26] previously referred to as 3 : 4 : 6 : 9-tetrahydro-7 : 8-benzindolo(2′ : 3′-1 : 2)-pyridocoline] in benzene was kept overnight at room temperature with excess of methyl iodide. The resulting precipitate of the *methiodide* separated from methanol as yellow prisms, m. p. 279° (decomp.) (Found: C, 57·35; H, 5·45. $C_{19}H_{18}N_2,CH_3I$ requires C, 57·65; H, 5·05%). When this was refluxed with excess of silver chloride in aqueous methanol it yielded the methochloride, which recrystallised from methanol–acetone. With concentrated nitric acid this gave a bright orange-yellow colour. In concentrated sulphuric acid it gave a yellow solution, changed to red on the addition of 1 drop of water and to intense blue-purple on the addition of potassium dichromate. The methopicrate formed orange-yellow prisms, m. p. 199°, from methanol.

*1-γ-Ethoxybutyrylisoquinoline.*—When 1-cyano*iso*quinoline [27] (2·7 g.) was treated with 3-ethoxypropylmagnesium bromide, as under (*b*) for the preparation of 2-γ-ethoxybutyrylpyridine, it afforded the *ketone* (2·2 g.), b. p. 170—175°/2 mm. (Found: C, 74·15; H, 7·4; N, 5·9. $C_{15}H_{17}O_2N$ requires C, 74·05; H, 7·0; N, 5·75%). This showed a scarcely detectable peak at 3341 cm.$^{-1}$, whereas when method (*a*) was used a large peak was observed, indicating the presence of the imine. The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as yellow needles, m. p. 163° (for analysis dried for 10 hr. at 120°/0·1 mm.) (Found: C, 59·4; H, 4·9. $C_{21}H_{21}O_5N_5$ requires C, 59·55; H, 4·95%).

*1 : 2 : 3 : 4-Tetrahydro-1-oxobenzo[a]pyridocolinium Bromide* (XVI).—Treatment of the ketone (1·09 g.) with hydrobromic acid yielded the *bromide* (0·8 g.) as a brown solid which when recrystallised from ethanol–acetone had m. p. 223—224° (Found: C, 55·95; H, 4·3. $C_{13}H_{12}ONBr$ requires C, 56·1; H, 4·3%). When this was reduced under Clemmensen conditions it gave a base, whose picrate had m. p. 184° (decomp.) (Found: C, 54·65; H, 4·9. $C_{13}H_{17}N,C_6H_3O_7N_3$ requires C, 54·8; H, 4·8%). The phenylhydrazone (0·7 g.) formed from the ketone (0·8 g.) separated from ethanol–ether as reddish-brown crystals, m. p. 279° (Found: C, 62·05; H, 5·05. $C_{19}H_{18}N_3Br$ requires C, 61·95; H, 4·9%). The corresponding *phenylhydrazone chloride* separated from ethanol–ether as brown prisms, m. p. 243—246° (Found: C, 63·1; H, 5·8. $C_{19}H_{18}N_3Cl,2H_2O$ requires C, 63·4; H, 6·1%). Light absorption of this chloride: (*a*) acid, $\lambda_{max.}$ 2430, 2650, and 4490 Å (log ε 4·65, 4·06, and 4·41), $\lambda_{min.}$ 2600 and 3600 Å (log ε 4·04 and 3·0); (*b*) alkaline, $\lambda_{max.}$ 2300, 2440, 3300, and 5120 Å (log ε 4·38, 4·38, 3·78, and 4·44), $\lambda_{min.}$ 2380, 3020, and 3760 Å (log ε 4·36, 3·60, and 3·22). The corresponding *phenylhydrazone nitrate* separated from ethanol as yellow needles, m. p. 237° (Found: C, 65·5; H, 5·55. $C_{19}H_{18}O_3N_4$ requires C, 65·15; H, 5·15%). The *phenylhydrazone picrate* separated from dimethylformamide–ethanol as orange needles, m. p. 200° (Found: C, 58·3; H, 4·45. $C_{25}H_{20}O_7N_6$ requires C, 58·15; H, 3·90%).

*2-γ-Ethoxybutyrylquinoline.*—For the preparation of 2-cyanoquinoline Henze's [28] method was found to be preferable to that of Kaufmann and Dändliker.[27] When this nitrile (2·6 g.) was treated with 3-ethoxypropylmagnesium bromide as under (*a*) for the preparation of 2-(γ-ethoxybutyryl)pyridine, the product (2·2 g.) appeared to consist mainly of the *imine*, b. p. 165°/0·5 mm.

[26] Swan, *J.*, 1949, 1720.
[27] Kaufmann and Dändliker, *Ber.*, 1913, **46**, 2924.
[28] Henze, *ibid.*, 1936, **69**, 1566.



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(Found: C, 74·15; H, 7·5. $C_{15}H_{18}ON_2$ requires C, 74·4; H, 7·45%), and showed a strong band at 3343 cm.$^{-1}$. Method (*b*), however, gave the *ketone* (2 g.), b. p. 190°/2 mm., in which this band was virtually absent (Found: N, 6·75. $C_{15}H_{17}O_2N$ requires N, 5·75%). The 2 : 4-*dinitrophenylhydrazone* melted at 148°, after softening at 138° (Found: C, 59·5; H, 5·0. $C_{21}H_{21}O_5N_5$ requires C, 59·55; H, 4·95%).

1 : 2 : 3 : 4-*Tetrahydro*-4-*oxobenzo*[c]*pyridocolinium Bromide* (XVII).—The above imine or ketone (1·9 g.) when refluxed for 21 hr. with acetic–hydrobromic acid yielded the *bromide* (1·6 g.) as brown cubes, m. p. 116—118° (from methanol–acetone) (Found: C, 47·05; H, 5·65. $C_{13}H_{12}ONBr,3H_2O$ requires C, 47·0; H, 5·4%). The *phenylhydrazone* separated from ethanol–ether as deep red crystals, m. p. 251—252° (Found: C, 59·0; H, 5·65. $C_{19}H_{18}N_3Br,H_2O$ requires C, 59·05; H, 5·2%); when dried for 16 hr. at 150°/0·1 mm. this melted at 260° (Found: C, 60·5; H, 4·9. $C_{19}H_{18}N_3Br,0·5H_2O$ requires C, 60·45; H, 5·05%). The *phenylhydrazone chloride* separated from ethanol–ether as dark, brick-red needles, m. p. 257—258° (Found: C, 62·85; H, 6·45. $C_{19}H_{18}N_3Cl,2H_2O$ requires C, 63·4; H, 6·1%). Light absorption: (*a*) acid, $\lambda_{max.}$ 2280, 2680, 3270, and 4570 Å (log ε 4·13, 3·96, 3·62, and 4·35), $\lambda_{min.}$ 2500, 2900, and 3670 Å (log ε 3·86, 3·43, and 3·24); (*b*) alkaline, $\lambda_{max.}$ 2290 and 4890 Å (log ε 4·14 and 4·27), $\lambda_{min.}$ 3390 Å (log ε 2·97). The phenylhydrazone nitrate separated from ethanol as red needles, m. p. 257—258° and the *phenylhydrazone picrate* from ethanol–acetone as yellow, silky needles, m. p. 245° (decomp.) (Found: C, 58·1; H, 4·05. $C_{25}H_{20}O_7N_6$ requires C, 58·15; H, 3·90%).

Thanks are offered to Professor M.-M. Janot for kindly supplying specimens of flavopereirine perchlorate and flavocoryline perchlorate, to Professor S. Sugasawa for 2-2′- and for 2-4′-pyridylindole (and its methiodide), which were used for absorption spectral measurements, to Professor P. Karrer for 3-ethyl-4-*iso*propylpyridine picrate; and to Patna University, Bihar, India, for study leave and a maintenance grant (to K. B. P.).

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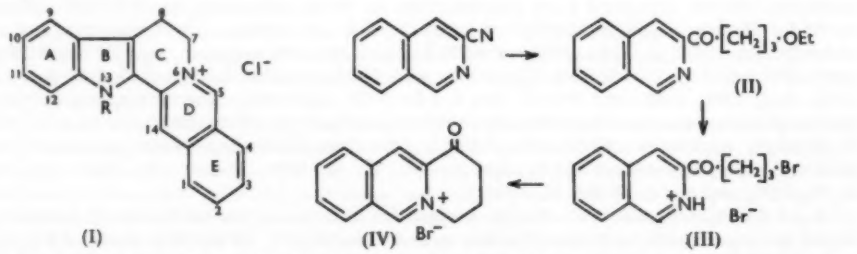
## 412. *The Constitution of Yohimbine and Related Alkaloids. Part XI.*[1] *A Synthesis of Sempervirine.*

By G. A. SWAN.

Syntheses of 7 : 8-dihydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride (I; R = H) and sempervirine (XIII) are described.

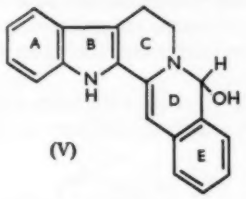
THE preceding paper [1] described a general method for the synthesis of compounds containing rings A, B, C, and D, of the yohimbine skeleton. In this paper, the method is extended to the synthesis of compounds containing also ring E and, in particular, of sempervirine (XIII).



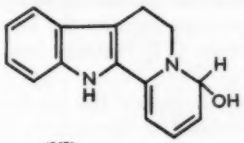

As a preliminary, 7 : 8-dihydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride (I; R = H) was synthesised. Acid hydrolysed the product of the action of 3-ethoxypropylmagnesium bromide on 3-cyano*iso*quinoline to crystalline 3-γ-ethoxybutyryl*iso*quinoline

[1] Prasad and Swan, preceding paper.

(II), showing no band in the 3370 cm.$^{-1}$ region (absence of NH). With hydrobromic–acetic acid this yielded a mixture of 3-$\gamma$-bromobutyryl*iso*quinoline hydrobromide (III) and its cyclisation product (IV); the former was converted into the latter by basification.



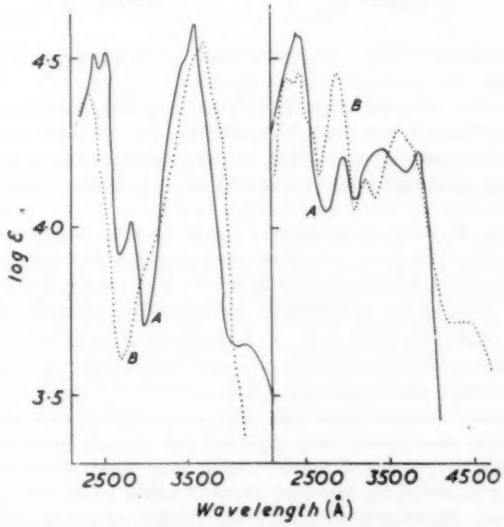

(V)




(VI)

The phenylhydrazone of the ketone (IV) in a Fischer indole reaction yielded 7 : 8-dihydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride (I; R = H), identical with a sample previously prepared by a different method.[2] The structure of the product was further

FIG. 1. FIG. 2.




*Absorption spectra of*: FIG. 1, 7 : 8-*dihydro*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium chloride*; FIG. 2 1 : 2 : 3 : 4-*tetrahydro*-13H-*benz*[g]*indolo*[a]*pyridocolinium nitrate*: *A, acid or neutral*; *B, alkaline.*

confirmed by the absorption of 2 mols. of hydrogen in the presence of Adams catalyst, with the formation of 5 : 7 : 8 : 13 : 13*b* : 14-hexahydrobenz[*g*]indolo[2 : 3-*a*]pyridocoline, identical with a sample prepared previously.[2]

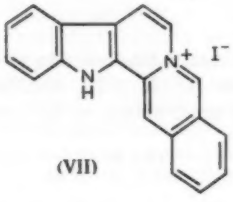
The absorption spectra of the product (I; R = H) in neutral and alkaline solution are shown in Fig. 1. The alkaline spectrum resembled that of 5 : 7 : 8 : 13-tetrahydrobenz-[*g*]indolo[2 : 3-*a*]pyridocoline [previously named 3 : 4-dihydro-7 : 8-benzindolo(2′ : 3′-1 : 2)-pyridocoline *] and this suggested the formation of the *pseudo*-base (V) in alkaline solution; this was confirmed by isolation of this pseudo-base as well as by the fact that the hydrogen atom attached to the indole nitrogen is not concerned with this change in alkaline solution. Thus, a Fischer indole reaction on the 1-methyl-1-phenylhydrazone of

* Owing to a typographical error, $\lambda_{max.}$ for this compound in ethanolic 0·01N-sodium hydroxide was given [2] as 3518 instead of 3718 Å.

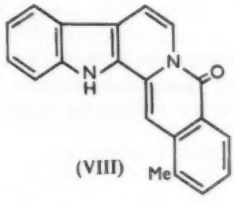
[2] Swan, *J.*, 1949, 1720.

the ketone (IV) gave the *N*-methyl compound (I; R = Me), the spectrum of which resembled that of the methyl-free compound (I; R = H) in both neutral and alkaline solution. This case differs from that of the 6 : 7-dihydro-12*H*-indolo[2 : 3-*a*]pyridocolinium salts described in the preceding paper, where anhydronium-base formation occurs in alkaline solution, perhaps because the loss of resonance energy associated with the formation of a pseudo-base (VI) becomes less important when the extra benzene ring (E) is present, as in (V).

Attempts to dehydrogenate the product (I; R = H) with tetrachloro-*o*-benzoquinone led to a product, isolated as the iodide, which was probably not obtained pure but was



(VII)



(VIII)

thought to have structure (VII). Its ultraviolet spectrum resembled that of dehydrooxoyobyrine [3] (VIII).

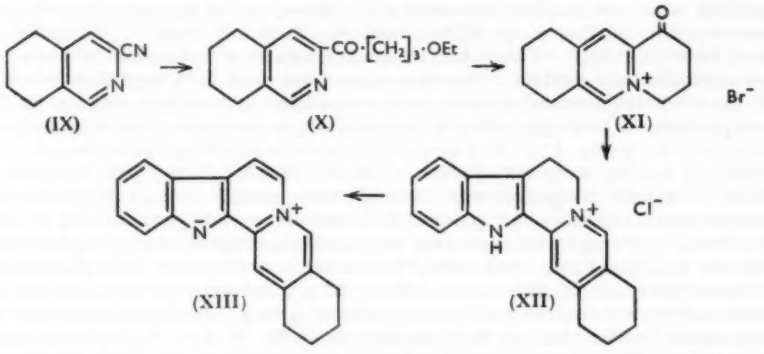
Although it has been reported [4] that Woodward and McLamore's [5] elegant synthesis of the sempervirine methosalts has been extended to the alkaloid itself, the latter work appears not to have been published. There has also been no report that Stevens's work [6] has yet culminated in the synthesis of sempervirine. A synthesis of the alkaloid is, however, now reported.

Although 3-chloro-5 : 6 : 7 : 8-tetrahydro*iso*quinoline is readily obtained from the 3-hydroxy-compound by the action of phosphorus oxychloride,[7] the use of the oxybromide gave mainly 3-bromo*iso*quinoline, instead of its 5 : 6 : 7 : 8-tetrahydro-derivative, which was desired for the preparation of a lithium derivative for reaction with $\gamma$-ethoxybutyronitrile to give 3-($\gamma$-ethoxybutyryl)-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (X). It was therefore necessary to prepare the latter by the action of 3-ethoxypropylmagnesium bromide on 3-cyano-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (IX). Stevens [6] (with Bentley) has worked out a method for the synthesis of the nitrile (IX) and, although this work has not yet been published, Dr. Stevens most generously supplied full experimental details. In the final stage of the synthesis, the required nitrile was accompanied by 3-cyano*iso*quinoline and purification was best achieved by repeated crystallisation from light petroleum. On one occasion, when it was attempted to purify the nitrile by chromatography on alumina which had not been specially dried, hydrolysis to the amide occurred.

Although the nitrile (IX) was carefully purified, the product from the Grignard reaction, mainly (X), contained 3-$\gamma$-ethoxybutyryl*iso*quinoline (II) and it appeared likely that some dehydrogenation had occurred during the reaction or in the subsequent isolation. However, these two ketones could be separated chromatographically and the pure compound (X) with hydrobromic–acetic acid gave 1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-octahydro-1-oxobenzo[*b*]-pyridocolinium bromide (XI); the phenylhydrazone of this readily underwent a Fischer indole reaction, giving 1 : 2 : 3 : 4 : 7 : 8-hexahydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium chloride (XII). The corresponding nitrate has recently been obtained by Wenkert and Roychaudhuri [8] by dehydrogenation of (±)-yohimb-15(20)-ene and its spectroscopic constants are in reasonable agreement with those of our product (XII) and its melting point

[3] Woodward and Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 2409.
[4] Saxton, *Quart. Rev.*, 1956, **10**, 108.
[5] Woodward and McLamore, *J. Amer. Chem. Soc.*, 1949, **71**, 379.
[6] Stevens, *Chem. Soc. Special Publn.* No. 3, 1955, p. 19.
[7] Schlittler and Merian, *Helv. Chim. Acta*, 1947, **30**, 1339.
[8] Wenkert and Roychaudhuri, *J. Amer. Chem. Soc.*, 1957, **79**, 1519.

agrees exactly with that of the nitrate derived therefrom. When this chloride was treated with an equimolecular amount of tetrachloro-*o*-benzoquinone in acetic acid and the resulting product was purified by chromatography and converted into a nitrate, it yielded 1 : 2 : 3 : 4-tetrahydro-13*H*-benz[*g*]indolo[2 : 3-*a*]pyridocolinium nitrate, identical with




sempervirine nitrate. The spectra of the product in neutral and alkaline solutions are shown in Fig. 2.

## Experimental

Ultraviolet absorptions were measured with a Hilger "Uvispec" spectrophotometer. Those referred to as "alkaline" were made in 0·015N-ethanolic potassium hydroxide and those referred to as "neutral" were in ethanol containing a trace of hydrochloric acid. Unless otherwise stated, "light petroleum" refers to a fraction of b. p. 60—80°, and analytical samples were dried at room temperature in a vacuum-desiccator.

3-*Cyano*isoquinoline.—Ethyl *iso*quinoline-3-carboxylate [9] (2·4 g.) when kept in aqueous ammonia (*d* 0·88; 24 ml.) for 2 days at room temperature, with occasional shaking, yielded *iso*quinoline-3-carboxyamide (2·02 g.), m. p. 212—213° (from water) (Found: C, 69·3; H, 4·9; N, 16·0. Calc. for $C_{10}H_8ON_2$: C, 69·75; H, 4·65; N, 16·3%). Case [10] gives m. p. 206° and Teague and Roe [11] give m. p. 213°. This (5 g.) was refluxed for 2 hr. with phosphorus oxychloride (12·5 ml.), the excess of the latter was removed (water-bath/reduced pressure) and the cooled residue was treated with chloroform and dilute sodium hydroxide solution. The chloroform extract was dried ($K_2CO_3$) and filtered and the solvent was removed. The residual nitrile, recrystallised from benzene–light petroleum (charcoal), yielded plates (2·65 g.), m. p. 124—125° (Found: C, 77·65; H, 3·95. Calc. for $C_{10}H_6N_2$: C, 77·95; H, 3·9%). Crowne and Breckenridge [12] give m. p. 127·5—128°. Light absorption in EtOH: $\lambda_{max.}$ 2310, 2790, 3080, and 3220 Å (log ε 4·76, 3·75, 3·39, and 3·52), $\lambda_{min.}$ 2530 Å (log ε 3·53).

3-*γ-Ethoxybutyryl*isoquinoline (II).—The above nitrile (0·64 g.) in ether (50 ml.) when treated with 3-ethoxypropylmagnesium bromide as for the preparation of 2-*γ*-ethoxybutyrylpyridine by method (*a*) of the preceding paper, except that the residue from the chloroform extract was not distilled but recrystallised from benzene–light petroleum (charcoal), gave the *ketone* (0·74 g.) as needles, m. p. 77—78° (Found: C, 74·05; H, 7·15; N, 6·15. $C_{15}H_{17}O_2N$ requires C, 74·1; H, 7·0; N, 5·75%). When this was treated with 2 : 4-dinitrophenylhydrazine in ethanol containing hydrobromic acid, the 2 : 4-dinitrophenylhydrazone bromide, m. p. 198—199°, separated. The latter, in chloroform solution, was treated with dilute sodium carbonate solution, and the residue from the chloroform extract was recrystallised from benzene–light petroleum; it yielded the bright red 2 : 4-*dinitrophenylhydrazone*, m. p. 158—159° (Found: C, 58·3; H, 5·1. $C_{21}H_{21}O_5N_5,0{\cdot}5H_2O$ requires C, 58·35; H, 5·1%).

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxobenzo*[b]*pyridocolinium Bromide* (IV).—The above ketone (0·74 g.) was refluxed for 15 hr. with 48% hydrobromic acid (1·5 ml.) and acetic acid (3 ml.). The

[9] Clemo and Hoggarth, *J.*, 1954, 95.
[10] Case, *J. Org. Chem.*, 1952, **17**, 471.
[11] Teague and Roe, *J. Amer. Chem. Soc.*, 1951, **73**, 688.
[12] Crowne and Breckenridge, *Canad. J. Chem.*, 1954, **32**, 641.

mixture was kept overnight at 0° and the resulting crystals A (0·32 g.; m. p. 160°) were collected and washed with acetone and ether. The filtrate was evaporated to dryness (water-bath/reduced pressure), the residue was dissolved in warm methanol, and the solution was diluted with acetone and allowed to cool. The resulting crystals B (0·47 g.) were washed with ether.

Crystals A, when recrystallised from methanol–acetone, yielded 3-*γ-bromobutyryl*iso*quinoline hydrobromide* (III), needles, m. p. 167° (Found: C, 38·20; H, 4·45. $C_{13}H_{13}ONBr_2,2{\cdot}5H_2O$ requires C, 38·6; H, 4·45%). This (0·1 g.) was shaken with ether and sodium carbonate (30 mg.) in water until all was in solution. The ether extract was dried for a short time ($Na_2SO_4$) and filtered, the ether was removed, and the residue was kept in chloroform solution for 2 hr. at room temperature. The residue left after removal of the chloroform was recrystallised from methanol–acetone, giving 1 : 2 : 3 : 4-*tetrahydro*-1-*oxobenzo*[b]*pyridocolinium bromide* (IV) as cream-coloured needles, m. p. 243° (Found: C, 56·45; H, 4·3. $C_{15}H_{12}ONBr$ requires C, 56·1; H, 4·3%). The same compound was obtained when crystals B were recrystallised from methanol–acetone (charcoal) and it appeared to be the sole product produced (0·9 g.) when the reaction mixture was evaporated to dryness, instead of being kept overnight in a refrigerator.

When the bromide (1·18 g.) was heated for 2·5 hr. on a water-bath with phenylhydrazine hydrochloride (0·8 g.), crystalline sodium acetate (2·7 g.), and water (38 ml.), and the mixture was cooled and filtered, it yielded the *phenylhydrazone* (1·32 g.), which separated from ethanol as orange-yellow needles, decomp. 285° (Found: C, 61·25; H, 4·7. $C_{19}H_{18}N_3Br$ requires C, 61·95; H, 4·9%). The corresponding *phenylhydrazone iodide* was obtained by adding potassium iodide solution to a hot solution of this bromide and separated from ethanol as orange needles, m. p. 281° (decomp.) (Found: C, 54·8; H, 5·35. $C_{19}H_{18}N_3I,C_2H_6O$ requires C, 54·7; H, 5·2%).

7 : 8-*Dihydro*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium Chloride* (I; R = H).—A mixture of the above phenylhydrazone (1 g.) and ethanol (40 ml.) was saturated with hydrogen chloride at 0°, kept for 2 hr. at room temperature, refluxed for 6 hr. and cooled in a refrigerator; the *chloride* (0·9 g.) separated and crystallised from absolute ethanol as orange-red needles, m. p. 330° (decomp.) (Found: C, 74·2; H, 5·25. $C_{19}H_{15}N_2Cl$ requires C, 74·4; H, 4·9%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2380, 2510, 2810, 3570, and 4180 Å (log ε, 4·52, 4·52, 4·02, 4·60, and 3·66), $\lambda_{min.}$ 2450, 2690, 2990, and 4090 Å (log ε 4·47, 3·91, 3·70, and 3·65); (*b*) alkaline, $\lambda_{max.}$ 2310, 3650 Å (log ε 4·40, 4·55), $\lambda_{min.}$ 2700 Å (log ε 3·60). The nitrate separated from ethanol as orange needles, m. p. 299° (decomp.).

The chloride (26 mg.) in acetic acid (4 ml.) absorbed 4·1 ml. of hydrogen at 18°/760 mm. during 2·25 hr. in the presence of freshly reduced Adams catalyst (23 mg.). The mixture was heated before removal of the catalyst and the filtrate was evaporated to dryness (water-bath/reduced pressure), the residue was basified with aqueous sodium hydroxide and extracted with ether, and the ether was removed from the dried ($K_2CO_3$) extract. The residue was recrystallised twice from benzene–light petroleum, then from aqueous ethanol, and again from benzene–light petroleum, affording 5 : 7 : 8 : 13 : 13*b*-14-hexahydrobenz[*g*]indolo[2 : 3-*a*]-pyridocoline as colourless needles, m. p. 197° alone or mixed with a specimen prepared by an earlier method.[2]

5 : 7 : 8 : 13-*Tetrahydro*-5-*hydroxybenz*[g]*indolo*[2 : 3-a]*pyridocoline* (V).—The precipitate formed on addition of dilute sodium hydroxide solution to an aqueous solution of the above chloride was collected, washed with water, and recrystallised from aqueous methanol, affording the brick-red pseudo-*base*, m. p. *ca.* 232° (decomp.) (for analysis dried for 19 hr. at 95°/0·1 mm.) (Found: C, 79·4; H, 5·35. $C_{19}H_{14}ON_2$ requires C, 79·15; H, 5·55%).

7 : 8-*Dihydro*-13-*methyl*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium Chloride* (I; R = Me).—1 : 2 : 3 : 4-Tetrahydro-1-oxobenzo[*b*]pyridocolinium bromide (0·24 g.) was treated with 1-methyl-1-phenylhydrazine (0·13 g.) and crystalline sodium acetate (0·6 g.) in N-hydrochloric acid (1·3 ml.) as described above for the phenylhydrazone. The resulting 1 : 2 : 3 : 4-*tetrahydro*-1-*oxobenzo*[b]*pyridocolinium* 1-*methyl*-1-*phenylhydrazone bromide* (0·2 g.) was recrystallised from ethanol and dried for 6 hr. at 90°/0·1 mm. (Found: C, 63·4; H, 4·9. $C_{20}H_{20}N_3Br$ requires C, 62·8; H, 5·25%). The corresponding iodide separated from ethanol–ether as orange-yellow plates, m. p. 344° (decomp.). The bromide (0·13 g.), in a Fischer indole reaction, yielded 7 : 8-*dihydro*-13-*methyl*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium chloride* (0·11 g.), separating from methanol as deep yellow needles, m. p. 315° (decomp.) (for analysis dried for 5 hr. at 110°/0·1 mm.) (Found: C, 70·85; H, 5·75. $C_{20}H_{17}N_2Cl,H_2O$ requires C, 70·9; H, 5·6%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2400, 2550, 2800, and 3520 Å (log ε 4·54, 4·56, 4·01, and

4·48), $\lambda_{min.}$ 2470, 2700, and 3000 Å (log ε 4·49, 3·93, and 3·75); (*b*) alkaline, $\lambda_{max.}$ 2200, 2310, and 3650 Å (log ε 4·33, 4·33, and 4·51), $\lambda_{min.}$ 2250 and 2750 Å (log ε 4·30 and 3·47).

A solution of the chloride (0·13 g.) and tetrachloro-*o*-benzoquinone (0·2 g.) in acetic acid (3 ml.) was heated on a water-bath for 3 hr., deposition of red needles beginning after a few minutes. The mixture was diluted with ether, and the red solid was collected and shaken with chloroform and N-sodium hydroxide. The chloroform extract was dried ($K_2CO_3$) and passed through a column of alumina. The residue from the eluate was dissolved in warm dilute hydrochloric acid and methanol, the solution was filtered and treated with one of potassium iodide, the bulk of the methanol was removed by distillation, and the solution then allowed to cool. The resulting precipitate recrystallised from aqueous methanol, affording a small amount of a chocolate-brown powder, m. p. *ca.* 211°, having in EtOH $\lambda_{max.}$ 2900 and 3450 Å (log ε 4·05 and 3·9; *M* assumed to be 400).

3-*Cyano*-5 : 6 : 7 : 8-*tetrahydroisoquinoline* (IX).—This was prepared from 5 : 6 : 7 : 8-tetrahydro-3-hydroxy*iso*quinoline according to the directions supplied by Dr. Stevens. The starting material was prepared by modification of existing methods.[13,14] Ethyl 5 : 6 : 7 : 8-tetrahydro-3-hydroxy*iso*quinoline-4-carboxylate, after recrystallisation from ethanol and sublimation at 155°/0·1 mm., had m. p. 168° (Found: C, 65·05; H, 7·1. Calc. for $C_{12}H_{15}O_3N$: C, 65·15; H, 6·8%). This ester (7·3 g.) was refluxed for 5 hr. with water (43 ml.) containing sodium hydroxide (5·8 ml.), and the solution was diluted with an equal volume of water, cooled, and treated with acetic acid (18 ml.). The resulting 5 : 6 : 7 : 8-tetrahydro-3-hydroxy*iso*quinoline-4-carboxylic acid, when recrystallised from ethanol, decomposed at 221° (Found: C, 61·65; H, 6·05. Calc. for $C_{10}H_{11}O_3N$: C, 62·05; H, 5·7%), and was decarboxylated at 230°; the resulting 5 : 6 : 7 : 8-tetrahydro-3-hydroxy*iso*quinoline, when recrystallised from ethanol, had m. p. 199° (3·95 g.). Light absorption of 3-cyano-5 : 6 : 7 : 8-tetrahydro*iso*quinoline in EtOH: $\lambda_{max.}$ 2675 Å (log ε 3·44).

*Reaction between* 5 : 6 : 7 : 8-*Tetrahydro-3-hydroxyisoquinoline and Phosphorus Oxybromide.*—The hydroxy-compound (1·93 g.) was heated for 18 hr. at 190° in a sealed tube with phosphorus oxybromide (17·5 ml.). The mixture was poured on ice, kept for 1 hr. at room temperature, and filtered and the filtrate was basified with solid sodium carbonate and extracted with ether. The dried ($K_2CO_3$) extract on distillation yielded an oil (1·8 g.), b. p. 170°/15 mm., a solution of which in ether was extracted repeatedly with a mixture of concentrated hydrochloric acid and water (1 : 1). The acid extract was basified with 40% aqueous sodium hydroxide and extracted with ether; the dried ($K_2CO_3$) extract on distillation yielded an oil (1·14 g.), b. p. 140°/2 mm., which set to a white solid. When the latter was recrystallised from benzene–light petroleum, then from light petroleum (b. p. 40—60°), sublimed at 55°/0·2 mm., and again crystallised from light petroleum, it yielded 3-bromo*iso*quinoline, as colourless needles, m. p. 61° (Found: C, 51·85; H, 3·0. Calc. for $C_9H_6NBr$: C, 51·9; H, 2·9%). For this compound Case [10] gives m. p. 63—64°. The material not extractable from ether with hydrochloric acid was recovered and separated from ethanol as white, silky needles, m. p. 144—145°, and appeared to be a *dibromo*iso*quinoline* (Found: C, 38·0; H, 1·95. $C_9H_5NBr_2$ requires C, 37·6; H, 1·75%).

5 : 6 : 7 : 8-*Tetrahydroisoquinoline-3-carboxyamide.*—A solution of the nitrile in light petroleum (b. p. 60—80°) was passed through a column of alumina, which was then eluted successively with light petroleum–benzene, benzene, benzene–ether, and ether; but the solute was still retained by the column. The material was finally removed by methanol, which yielded the *amide*, m. p. 195—196°, as colourless crystals from ethanol, the m. p. being unchanged by sublimation at 100°/0·1 mm. (Found: C, 67·8; H, 6·7. $C_{10}H_{12}ON_2$ requires C, 68·2; H, 6·8%).

3-*γ-Ethoxybutyryl*-5 : 6 : 7 : 8-*tetrahydroisoquinoline* (X).—A solution of 3-cyano-5 : 6 : 7 : 8-tetrahydro*iso*quinoline (1·1 g.) in ether (25 ml.) was treated with a Grignard reagent prepared from magnesium (0·7 g.), 3-ethoxypropyl bromide (4 g.), and ether (20 ml.) as described under (*a*) for the preparation of 2-γ-ethoxybutyrylpyridine in the preceding paper, the product being a yellow, viscous oil (1·45 g.), b. p. 190° (bath-temp.)/4 mm. The latter was dissolved in a small volume of light petroleum (b. p. 40—60°) and kept in a refrigerator, crystals separating. These were collected, washed with light petroleum (b. p. 40—60°), and recrystallised from the same solvent, affording colourless needles (32 mg.), m. p. 50—58° (Found: C, 71·4; H, 8·35%).

The petroleum solutions containing the remainder of the product were passed through a column of alumina (20 g.), which was then eluted successively with (1) light petroleum (b. p.

[13] Basu and Banerjee, *Annalen*, 1935, **516**, 243.
[14] Swiss P. 253,710.

40—60°), (2) light petroleum–benzene (10 : 1), (3) benzene, and (4) benzene–ethanol (10 : 1). By evaporation of these fractions the following residues were obtained: (1) 0·67 g. of material which, when dissolved in a very small volume of light petroleum (b. p. 40—60°) and kept at 0°, deposited prisms, m. p. 24—25°; (2) 0·17 g., apparently essentially the same as (1); (3) 0·25 g. of material which, when recrystallised from light petroleum (b. p. 40—60°), yielded 3-*γ*-ethoxybutyryl*iso*quinoline (II), as needles, m. p. 75°, identified by comparison of its infrared spectrum with that of an authentic sample and by analysis (Found: N, 5·9. Calc. for $C_{15}H_{17}O_2N$: N, 5·75%); and (4) a brown oil which, when distilled, gave an oil (0·25 g.), b. p. 150—210° (bath-temp.)/1 mm. Fractions (1) and (2) were combined and distilled, giving a colourless oil (0·6 g.), b. p. 180—190° (bath-temp.)/1 mm., apparently 3-*γ-ethoxybutyryl*-5 : 6 : 7 : 8-*tetrahydro*-iso*quinoline* (X), which showed no band in the 3370 cm.$^{-1}$ region (Found: C, 72·55; H, 8·8; N, 5·7. $C_{15}H_{21}O_2N$ requires C, 72·9; H, 8·5; N, 5·65%).

1 : 2 : 3 : 4 : 7 : 8 : 9 : 10-*Octahydro*-1-*oxobenz*[b]*pyridocolinium Bromide* (XI).—The ketone (X) (0·55 g.) was refluxed for 12·5 hr. in an atmosphere of nitrogen with 48% hydrobromic acid (2 ml.) and acetic acid (4 ml.), and the solution was evaporated to dryness, but the residue failed to crystallise. It was therefore converted, in the usual manner, into the *phenylhydrazone* (0·75 g.), which separated from ethanol–ether as orange crystals, m. p. 285° (decomp.) (Found: C, 60·55; H, 7·0. $C_{19}H_{23}N_3Br,C_2H_6O$ requires C, 60·3; H, 6·7%).

1 : 2 : 3 : 4 : 7 : 8-*Hexahydro*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium Chloride* (XII).—The above phenylhydrazone (0·64 g.) was subjected to a Fischer indole reaction as described previously, and the mixture was concentrated to one-third of its volume and kept at 0°. The resulting solid (0·55 g.) when recrystallised from ethanol gave the orange-yellow *chloride*, m. p. 324° (decomp.) (for analysis dried for 7 hr. at 100°/0·1 mm.) (Found: C, 71·2; H, 6·15. $C_{19}H_{19}N_2Cl,0·5H_2O$ requires C, 71·35; H, 6·25%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2230, 3190, and 3850 Å (log ε 4·37, 4·25, and 4·15), $\lambda_{min.}$ 2750 and 3480 Å (log ε 3·41 and 3·99); (*b*) alkaline, $\lambda_{max.}$ 2320, 2650, 3600, and 4060 Å (log ε 4·41, 3·99, 4·19, and 4·17), $\lambda_{min.}$ 2550, 2900, and 3850 Å (log ε 3·95, 3·38, and 4·15). The nitrate separated from aqueous ethanol as orange needles, m. p. 305—306° (decomp.).

1 : 2 : 3 : 4-*Tetrahydro*-13H-*benz*[g]*indolo*[2 : 3-a]*pyridocolinium Nitrate*.—The above chloride (40 mg.) in acetic acid (0·5 ml.) was heated with tetrachloro-*o*-benzoquinone (40 mg.) for 3 hr. on a water-bath and the mixture was diluted with ether. The resulting solid was shaken with chloroform and dilute sodium hydroxide solution, and the chloroform extract was dried ($K_2CO_3$) and passed through a column of alumina (5 g.), which was then eluted with chloroform, the eluate being collected in 17 equal fractions. The first two fractions yielded a small amount of residue which, in dilute ethanolic solution, gave a greenish-yellow fluorescence; but the residues from the remaining fractions gave a brilliant blue fluorescence. The latter residues (15) were combined and warmed with dilute hydrochloric acid, and the solution was filtered and treated with saturated sodium nitrate solution; a slightly brownish-yellow precipitate (20 mg.) was then formed. This was collected, washed with water, and recrystallised from methanol, giving the *nitrate*, m. p. 267° (decomp.) (Found: C, 65·35; H, 5·15. $C_{19}H_{17}O_3N_3,0·75H_2O$ requires C, 65·4; H, 5·3%). Light absorption: (*a*) neutral, $\lambda_{max.}$ 2430, 2480, 2970, 3460, and 3860 Å (log ε 4·58, 4·57, 4·21, 4·23, and 4·22), $\lambda_{min.}$ 2760, 3110, and 3700 Å (log ε 4·04, 4·08, and 4·16); (*b*) alkaline, $\lambda_{max.}$ 2300, 2450, 2890, 3220, 3620, and 4350 Å (log ε 4·44, 4·46, 4·46, 4·14, 4·29, and 3·72), $\lambda_{min.}$ 2370, 2680, 3100, 3330, and 4250 Å (log ε 4·43, 4·15, 4·05, 4·08, and 3·71). The infrared spectrum was almost indistinguishable from that of a sample of sempervirine nitrate of natural origin.

Light absorption of sempervirine methiodide in EtOH: $\lambda_{max.}$ 2420, 2950, 3380, and 3950 Å (log ε 4·53, 4·21, 4·29, and 4·22), $\lambda_{min.}$ 2800, 3100, and 3700 Å (log ε 4·11, 4·06, and 4·07).

Thanks are offered to Dr. T. S. Stevens for his kindness in supplying details of the preparation of 3-cyano-5 : 6 : 7 : 8-tetrahydro*iso*quinoline before publication.

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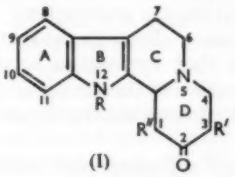
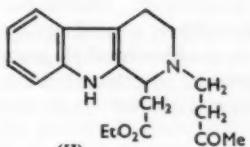
## 413. *The Constitution of Yohimbine and Related Alkaloids. Part XII.* Some Unsuccessful Synthetic Approaches to Yohimbine and Alstoniline.*

By K. B. Prasad and G. A. Swan.

Dieckmann cyclisation of diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-propionate has been shown to yield mainly the ester (I; R = R′ = H, R″ = $CO_2Et$) and is therefore not of value for synthetic work in the yohimbine field. The ketone (III) was synthesised, but did not prove a useful intermediate. β-*o*-(Methoxymethyl)phenylalanine (VI) has also been synthesised.

Groves and Swan [1] synthesised the ketone (I; R = R′ = R″ = H), but were unable to introduce into position 3 a substituent suitable for building up of ring E of yohimbine and related alkaloids. This ketone was obtained by a Dieckmann reaction on diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-propionate, followed by hydrolysis and decarboxylation of the crude reaction product, which probably contained both isomeric β-keto-esters (I; R = R′ = H, R″ = $CO_2Et$, and R = R″ = H, R′ = $CO_2Et$). We have now fractionated the product at the β-keto-ester stage, though the homogeneity of our crystalline material is uncertain and attempts to build up ring E by treating this material with 4-diethylaminobutan-2-one methiodide were unsuccessful. We therefore repeated the synthesis of the diesters, using ethyl [*carboxy*-$^{14}$C]acrylate, and isolated two radioactive fractions of the β-keto-ester formed by its cyclisation. If the material consisted of (I; R = R″ = H, R′ = $CO_2Et$) then on hydrolysis it should yield inactive ketone, with the


(I)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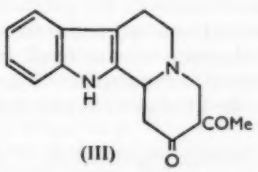

(III)

evolution of strongly radioactive carbon dioxide; if it were (I; R = R′ = H, R″ = $CO_2Et$), the ketone formed should be active and the evolved carbon dioxide inactive. The measured relative activities of the products from the two fractions of β-keto-ester were comparable and suggest that the reaction product contained only about 15% of the desired (I; R = R″ = H, R′ = $CO_2Et$). It was thought that this unfavourable ratio might be improved by introducing a benzyl substituent (R) (which might be removable at a later stage). Some intermediates towards the possible synthesis of 1-benzyltryptamine by extension of Speeter and Anthony's method [2] are described in the Experimental section; but the base used was prepared by a different method.[3] However, this base failed to condense satisfactorily with 1-ethyl 4-hydrogen 2-oxosuccinate and this approach was abandoned.

Ethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate underwent a Mannich reaction with acetone and formaldehyde to give the ester (II), which by Dieckmann reaction gave the pyridocoline (III). Here again we were unsuccessful in our attempts to build up ring E by the use of 4-diethylaminobutan-2-one methiodide, as ring D opened very readily. In other work we synthesised the amine (IV) but we were unable to isolate the pyridone (V) after an attempted Dieckmann reaction. We had also thought that the pyridocoline (III) (or the enol-ether formed by methylating it) might condense with ethyl cyanoacetate to

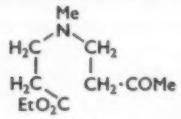
* Part XI, preceding paper.

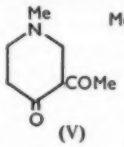
[1] Groves and Swan, *J.*, 1952, 650.
[2] Speeter and Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6208.
[3] U.S.P. 2,642,438.

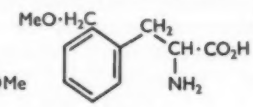
give a product containing a pyranone ring (E), which could be used for the synthesis of alkaloids of the alstonine type. However, our attempts to condense 2-acetyl*cyclo*hexanone with ethyl cyanoacetate in the presence of sodium ethoxide apparently gave ethyl 6-oxoheptane-1-carboxylate.

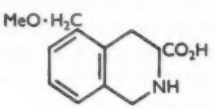
Mild alkaline hydrolysis of the condensation product of 3-methylenepentan-2-one with ethyl oxalate gave 5-methylene-2 : 4-dioxoheptanoic acid; but we were unable to condense this with tryptamine to yield the ketone (I; R = R″ = H, R′ = Et).

Our main interest in these experiments had been the hope that they might open the way to the synthesis of compounds containing the methoxycarbonyl group of yohimbine and alstoniline. After their failure, we turned to the synthesis of β-*o*-(methoxymethyl)phenylalanine (VI), hoping that this might condense with formaldehyde to give the quinoline (VII), which could be subjected to a series of reactions previously carried out on 1 : 2 : 3 : 4-


(IV)


(V)


(VI)


(VII)

tetrahydro*iso*quinoline-3-carboxylic acid,[4 5] with subsequent conversion of the methoxymethyl group into a methoxycarbonyl group.[6] *o*-Methoxymethylbenzyl chloride was condensed with ethyl acetamidomalonate and the product was hydrolysed to β-*o*-methoxymethylphenylalanine. Attempts to condense this with formaldehyde in the presence of hydrochloric acid, however, led to 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid. The mechanism of this reaction is not clear. During the reaction, the amino-group would be present as a salt and therefore unlikely to undergo cyclisation. Perhaps the methoxymethyl group is converted into a chloromethyl group so that cyclisation occurs on subsequent evaporation. The product of attempted esterification of the amino-acid with ethanolic hydrogen chloride is likewise ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate.

*o*-(Methoxymethyl)benzyl chloride condensed with diethyl malonate, and hydrolysis and decarboxylation of the product yielded β-(*o*-methoxymethyl)phenylpropionic acid. Attempts to cyclise the acid gave non-ketonic products.

## Experimental

*Dieckmann Cyclisation of Diethyl* 1 : 2 : 3 : 4-*Tetrahydro*-β-*carboline*-1-*acetate*-2-*propionate*.—The reaction was carried out on the diester (1·2 g.) as described by Groves and Swan,[1] except that the hydrolysis was omitted and at the end of the reaction the cooled mixture was treated with water and the benzene layer was shaken with 10% sodium hydroxide solution. The combined aqueous layers were extracted with benzene, then neutralised with acetic acid and the resulting gum was taken up in chloroform. The solvent was removed from the dried ($Na_2SO_4$) extract and a solution of the residue in benzene and light petroleum was poured through a column of alumina. Development was begun with benzene containing 1% of ethanol and the residue from the eluate, when recrystallised from light petroleum, gave a pale yellow solid (90 mg.), m. p. 126—128°, after sintering at 120°. This was dissolved in hot, light petroleum. On cooling, clusters of almost colourless needles separated; but when the solution was then placed in a refrigerator, deep yellow prisms also separated. On subsequent attempts to obtain only the colourless needles, the deep yellow prisms always separated and the *product* had m. p. 128—129° (Found: C, 69·65; H, 6·65. $C_{18}H_{20}O_3N_2$ requires C, 69·25; H, 6·4%). Development of the chromatogram was continued with benzene containing 4% of ethanol, yielding a bright yellow solid (170 mg.), m. p. 115—117°, after sintering at 110°.

A similar experiment in which the product was crystallised from benzene–light petroleum,

[4] Clemo and Swan, *J.*, 1946, 617.
[5] Swan, *J.*, 1949, 1720.
[6] Cf. Elderfield and Wythe, *J. Org. Chem.*, 1954, **19**, 683.

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without chromatography, yielded a bright yellow substance, m. p. 115—116° (Found: C, 69·2; H, 6·8%).

An attempt to alkylate the keto-ester with 4-diethylaminobutan-2-one methiodide in the presence of methanolic sodium methoxide [7] gave, as the only pure products 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-octahydro-2-ketoindolo[2 : 3-*a*]pyridocoline and *dimethyl* 1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*-1-*acetate*-2-*propionate*, colourless prisms, m. p. 140° (from benzene–light petroleum) (Found: C, 66·1; H, 6·85. $C_{18}H_{22}O_4N_2$ requires C, 65·45; H, 6·65%). The latter compound (mixed m. p. not depressed) was also obtained by refluxing the diethyl ester for a few hours with anhydrous methanol containing a trace of sodium methoxide.

*Experiment using Ethyl* [carboxy-$^{14}$C]*Acrylate*.—Potassium [$^{14}$C]cyanide, prepared from barium [$^{14}$C]carbonate (5 μc) by McCarter's method,[8] was diluted with inactive sodium cyanide (2·7 g.) and gradually added to a refluxing solution of ethylene chlorohydrin (5 g.) in ethanol (15 ml.), being washed in with further ethanol (12 ml.). The mixture was refluxed for 8 hr., kept overnight at room temperature, diluted with ether (20 ml.), and filtered and the filter cake was washed with ethyl acetate. On distillation the fraction (3·23 g.) of b. p. 110°/15 mm. was collected and redistilled, with a little inactive hydracrylonitrile as " chaser ".

Copper bronze (0·17 g.) and absolute ethanol (5·3 g.) were mixed, cooled with water, and treated gradually with a mixture of concentrated sulphuric acid (3·6 ml.) and water (0·75 ml.). The above nitrile (3·58 g.) was then added and the mixture was stirred and its temperature was raised to 130° during 35 min.; distillation began, and the temperature was then raised to 150° during a further 1 hr. The residue was allowed to cool and diluted with ethanol (3·6 ml.) and its temperature was again raised to 130°, then to 170° during 100 min. The combined distillates were shaken with 6 vols. of saturated brine, dried ($CaCl_2$), and distilled, giving ethyl [*carboxy*-$^{14}$C]-acrylate (1·78 g.), b. p. 98—100°. The low-boiling fraction of the distillate, when shaken with 6 vols. of saturated brine, dried, and distilled, yielded a further amount (0·07 g.) of ester. The combined product was redistilled, with the addition of inactive ethyl acrylate (1·3 g.), giving 2·78 g. of product, b. p. 98—100°.

This ester was heated in a sealed tube for 15 hr. at 134° with ethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate (2·2 g.). The product was evaporated to dryness (water-bath/reduced pressure), and the residue was dissolved in ether, treated with ethanolic hydrogen chloride, and stirred until crystallisation occurred. The resulting precipitate was collected, washed with ether, and recrystallised from ethanol, giving a hydrochloride (2·48 g.; m. p. 147—148°) which yielded a base, m. p. 76—78° (0·5 g.) (from benzene–light petroleum). This, diluted with inactive diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-propionate (0·7 g.), in dry benzene was added to alcohol-free sodium ethoxide (from sodium, 0·11 g.) and the mixture was refluxed for 4·5 hr. in nitrogen. After cooling, the mixture was treated with water and the benzene layer extracted with dilute sodium hydroxide solution. The combined aqueous extracts were extracted with ether, adjusted to pH 5 with acetic acid, and extracted with chloroform. The dried ($Na_2SO_4$) chloroform extract yielded a gum (0·67 g.) which was extracted with boiling light petroleum (b. p. 60—80°) (70 ml.), leaving a gum A (0·34 g.). The petroleum solution was kept overnight at room temperature, decanted from a small amount of bright yellow solid, concentrated to 10 ml., and kept overnight at 0°. The resulting pale yellow crystals (0·28 g.; m. p. 102—119°) were recrystallised twice from light petroleum (b. p. 60—80°), giving B (0·17 g.; m. p. 123—125°). The residue A was extracted further with boiling light petroleum, and the resulting extracts were combined with the mother-liquor from which the crystals (0·28 g.; m. p. 102—119°) had been filtered and the mixture was concentrated to 10 ml. On cooling, further crystals C (0·1 g.; m. p. 117—118°) separated.

The crystals C (50 mg.) were refluxed with N-hydrochloric acid (8 ml.) for 4 hr., during which nitrogen was passed first through the refluxing solution, then through three bubblers containing carbonate-free sodium hydroxide solution. The carbonate collected was precipitated in the usual manner as barium carbonate (34·5 mg.). The acidic, hydrolysed solution was evaporated to dryness (water-bath/reduced pressure), and the residue dissolved in water, basified with sodium hydroxide solution, and extracted with chloroform. The residue from the extract was recrystallised from benzene, affording the ketone, m. p. 178—180°. When material B (51·0 mg.) was similarly hydrolysed, barium carbonate (33·6 mg.) was obtained. The samples B and C and the ketones obtained by hydrolysis of them were burnt and the specific activities of the

[7] du Feu, McQuillin, and Robinson, *J.*, 1937, 53.
[8] McCarter, *J. Amer. Chem. Soc.*, 1951, **73**, 483.

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resulting carbon dioxide, as well as that liberated by acidification of the barium carbonate samples, were measured by the gas-counting method [9] for $^{14}CO_2$.

*Ethyl* 1 : 2 : 3 : 4-*Tetrahydro*-2-3′-*oxobutyl*-β-*carboline*-1-*acetate* (II).—Ethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate hydrochloride (2·4 g.), paraformaldehyde (0·4 g.), acetone (8 ml.), and ethanol (8 ml.) were refluxed for 5 hr., then evaporated to give a gum, which was dissolved in water and basified with aqueous sodium hydroxide. The base was collected, washed with water, dried in a vacuum-desiccator, and recrystallised from benzene–light petroleum, giving the *keto-ester* (2·12 g.), prisms, m. p. 143—144° (Found: C, 69·15; H, 7·5. $C_{19}H_{24}O_3N_2$ requires C, 69·5; H, 7·3%).

3-*Acetyl*-1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-*octahydro*-2-*oxoindolo*[2 : 3-a]*pyridocoline* (III).—The above keto-ester (2·12 g.) was added to alcohol-free sodium ethoxide (0·7 g.) suspended in benzene (50 ml.), and the mixture was refluxed for 2·75 hr. in nitrogen, cooled, and treated with water. The organic layer was washed with dilute sodium hydroxide solution. The combined aqueous layers were extracted with ether, then exactly neutralised with dilute acetic acid, a pale buff precipitate being produced. This (1·62 g.) was collected, washed with water, dried, and recrystallised from benzene, giving the *diketone* (1·3 g.) as cream-coloured leaflets, m. p. 205—206° (Found: C, 72·5; H, 6·45. $C_{17}H_{18}O_2N_2$ requires C, 72·35; H, 6·4%).

*Methylation of the Above Diketone.*—Treatment of a solution of the diketone in N-sodium hydroxide with methyl sulphate yielded a precipitate which, after being washed with water, dried, and boiled first with methanol, then with benzene, had m. p. 192° (Found: C, 72·15, 72·25, 71·9, 71·65; H, 7·0, 7·35, 7·55, 7·35%). The same *product* (Found: C, 72·1; H, 6·9%) was obtained by treatment of the diketone with diazomethane.

N-2-*Cyanoethyl*-N-3-*oxobutylmethylamine.*—A mixture of *N*-2-cyanoethylmethylamine (12·1 g.), ethanol (30 ml.), concentrated hydrochloric acid (15 ml.), paraformaldehyde (7·5 g.), and acetone (30 ml.) was refluxed for 6 hr., the solvents were removed, and the residue was cooled and treated with water and saturated potassium carbonate solution and extracted with ether. The dried ($K_2CO_3$) extract on distillation gave the tertiary *base* (19·9 g.), b. p. 140—150°/12 mm. (Found: C, 62·5; H, 9·25. $C_8H_{14}ON_2$ requires C, 62·35; H, 9·1%).

*Ethyl* β-(N-*Methyl*-N-3-*oxobutylamino*)*propionate* (IV).—A solution of the above nitrile (25·25 g.) in absolute ethanol (100 ml.) was saturated with hydrogen chloride at 0°, kept overnight at room temperature, refluxed for 4 hr., and evaporated to a small volume. The *ester* (14 g.), b. p. 130°/14 mm., was isolated by extraction with ether, after basification with potassium carbonate (Found: C, 59·35; H, 9·55. $C_{10}H_{19}O_3N$ requires C, 59·7; H, 9·45%).

3-2′-*Phthalimidoethylindole.*—Tryptamine (0·5 g.) and phthalic anhydride (0·5 g.) were heated for 3 hr. at 180—190° and the *product* was recrystallised alternately from benzene and ethanol, giving plates, m. p. 164° (Found: C, 74·2; H, 5·3. $C_{18}H_{14}O_2N_2$ requires C, 74·5; H, 4·85%).

1-*Benzylindol*-3-*ylglyoxylyl Chloride.*—This *chloride* was prepared from 1-benzylindole by Speeter and Anthony's method [2] and separated from benzene–light petroleum as yellow prisms, m. p. 105° (Found: C, 68·0; H, 4·35. $C_{17}H_{12}O_2NCl$ requires C, 68·55; H, 4·05%).

1-*Benzylindol*-3-*ylglyoxylamide.*—The above chloride with ethereal ammonia gave the *amide*, needles (from ethanol), m. p. 186° (for analysis dried for 5 hr. at 90°/0·1 mm.) (Found: C, 73·15; H, 5·25; N, 10·5. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·05; N, 10·05%).

1 : N : N-*Tribenzylindol*-3-*ylglyoxylamide.*—The chloride (0·1 g.) was treated with ethereal dibenzylamine (0·2 g.), and the *product* was extracted with dilute hydrochloric acid and crystallised from ethanol as needles, m. p. 143—144° (Found: C, 80·9; H, 5·85. $C_{31}H_{26}O_2N_2$ requires C, 81·2; H, 5·7%).

The *monobenzylamino-compound*, prepared similarly, separated from ethanol as needles, m. p. 172—173° (Found: C, 72·7, 72·6, 72·7; H, 5·05, 5·35, 5·2. $C_{17}H_{14}O_2N_2,0{\cdot}25C_2H_6O$ requires C, 72·5; H, 5·35%).

γ-*Formamidobutaldehyde* 1-*Benzyl*-1-*phenylhydrazone.*—This was prepared from 1-benzyl-1-phenylhydrazine and γ-formamidobutaldehyde diethyl acetal [11] and separated from light petroleum (b. p. 40—60°) as needles, m. p. 74—75° (Found: C, 73·35; H, 7·55. $C_{18}H_{21}ON_3$ requires C, 73·25; H, 7·1%).

[9] Swan, *J.*, 1955, 1039.
[10] Plieninger, *Chem. Ber.*, 1954, **87**, 127.
[11] Wohl, Schäfer, and Thiele, *Ber.*, 1905, **38**, 4159.

*Attempted Condensation of* 2-*Acetyl*cyclo*hexanone with Ethyl Cyanoacetate*.—Ethyl cyanoacetate (1·13 g.), followed by 2-acetyl*cyclo*hexanone [12] (1·4 g.) was added to a solution of sodium (0·23 g.) in absolute ethanol, and the solution was heated for 1·5 hr. on a water-bath, kept overnight at room temperature, treated with water containing concentrated hydrochloric acid (1·3 ml.) and extracted with ether. The extract was washed with water, dried ($Na_2SO_4$), and distilled, yielding ethyl 6-oxoheptane-1-carboxylate, b. p. 120° (bath-temp.)/2 mm. (Found: C, 64·35; H, 9·9. Calc. for $C_{10}H_{18}O_3$: C, 64·5; H, 9·7%).

*Ethyl* 2-2′-*Cyanoethyl*-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*-1-*acetate*.—As the paragraph of this heading on p. 656 of the paper by Groves and Swan [1] is inaccurate, this paragraph is intended as a correction. A mixture of ethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate (from the hydrochloride, 0·8 g.) and vinyl cyanide (2 ml.) was heated in a sealed tube for 22 hr. at 125°, the excess of vinyl cyanide was removed and the residue was stirred with ether, giving the *base* (0·5 g.), which when recrystallised from benzene containing a small proportion of light petroleum (b. p. 40—60°) had m. p. 130° (Found: C, 69·15; H, 6·7; N, 14·0. $C_{18}H_{21}O_2N_3$ requires C, 69·45; H, 6·75; N, 13·5%). When this was refluxed with ethanolic sodium hydroxide solution, the solution diluted with water, the ethanol removed, and the solution then acidified with acetic acid, it yielded 1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*-1-*acetic*-2-*propionic acid*, m. p. 219° (decomp.) (Found: C, 61·45; H, 6·05. $C_{16}H_{18}O_4N_2,0·5H_2O$ requires C, 61·75; H, 6·1%). The same acid was obtained by saponification of diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-propionate.

3-2′-(2-*Cyanoethylamino*)*ethylindole*.—Tryptamine (0·1 g.) was refluxed for 13 hr. with vinyl cyanide (1·5 ml.), the excess of the latter was removed, and a solution of the residue in ether was treated with ethanolic hydrogen chloride. The resulting precipitate was stirred with ether and recrystallised from ethanol–acetone–ether, giving the *indole*, m. p. 185° (Found: C, 62·4; H, 6·45; N, 16·95. $C_{13}H_{15}N_3$,HCl requires C, 62·5; H, 6·4; N, 16·8%).

5-*Methylene*-2 : 4-*dioxoheptanoic Acid*.—Ethyl oxalate (1·5 ml.) followed by 3-methylenepentan-2-one [13] (1 ml.) was added to sodium ethoxide (0·7 g.) in ether (20 ml.). The mixture became homogeneous and was kept for 3 days at room temperature before being diluted with water. The organic layer was extracted with dilute sodium hydroxide solution, and the combined alkaline layers were acidified and extracted with ether. The residue left on removal of the ether from the latter extract was kept in N-sodium hydroxide (5 ml.) for 1·5 hr. at room temperature, then acidified. The *acid* (0·2 g.) was precipitated; from carbon tetrachloride it formed cream-coloured crystals, m. p. 55—57°, giving an intense red colour with ferric chloride (Found: C, 56·2; H, 6·0. $C_9H_{10}O_4$ requires C, 56·5; H, 5·9%).

1-*Ethyl* 4-*Hydrogen* 2-*Oxosuccinate*.—Shaking diethyl sodio-oxaloacetate (20 g.) with water (150 ml.) and N-sodium hydroxide (150 ml.) for 10 min. and working up the whole as described by Groves and Swan [1] gave the acid in yields varying between 8 and 10 g.

α-*Ethoxycarbonyladiponitrile*.—Ethyl cyanoacetate (3·9 ml.) and γ-bromobutyronitrile (4·8 g.) were added to a solution of sodium (0·75 g.) in ethanol (20 ml.), the mixture refluxed for 6·5 hr., then cooled and filtered, and the ethanol removed from the filtrate. The residue was treated with water, acidified with acetic acid, and extracted with ether. Distillation of the dried ($Na_2SO_4$) extract gave the *nitrile* (2 g.), b. p. 170—175°/2 mm. (Found: C, 59·95; H, 6·8; N, 15·3. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·65; N, 15·55%).

*Diethyl Acetamido*-o-(*methoxymethyl*)*benzylmalonate*.—Diethyl acetamidomalonate [14] (29·7 g.) was added with stirring to a solution of sodium (3·2 g.) in absolute ethanol (175 ml.), followed by *o*-(methoxymethyl)benzyl chloride [15] (23·3 g.) in ethanol (25 ml.) during 10 min. The mixture was stirred and refluxed for 15 hr., then filtered, and the filter cake was washed with hot ethanol. The solvent was removed from the combined ethanolic solution (water-bath/reduced pressure), and the residue stirred with water until it crystallised. When recrystallised from water (1 l. per 10 g.) the *ester* (33·8 g.) formed needles, m. p. 73—74° (Found: C, 61·25; H, 7·1. $C_{18}H_{25}O_6N$ requires C, 61·55; H, 7·1%).

N-*Acetyl*-β-o-(*methoxymethyl*)*phenylalanine*.—The above ester (6 g.) was refluxed for 4 hr. with 10% aqueous sodium hydroxide (40 ml.). The solution was cooled, mixed with 3N-hydrochloric acid (40 ml.), refluxed for 1 hr., and filtered hot. The *acid* which separated on cooling

[12] Meerwein and Vossen, *J. prakt. Chem.*, 1934, **141**, 149.
[13] Colonge and Cumet, *Bull. Soc. chim. France*, 1947, 838.
[14] Vignau, *ibid.*, 1952, 638.
[15] Mann and Stewart, *J.*, 1954, 2819.

crystallised from aqueous ethanol and had m. p. 158° (3·5 g.) (Found: C, 61·85; H, 7·0. $C_{13}H_{17}O_4N$ requires C, 62·15; H, 6·75%).

β-(o-*Methoxymethyl*)*phenylalanine* (VI).—The above acetyl compound (3·5 g.) was refluxed for 10 hr. with water (42·5 ml.) and concentrated sulphuric acid (2·5 ml.). The cooled solution was treated with a slight excess of barium hydroxide solution and filtered. The filtrate was saturated with carbon dioxide, then heated on a water-bath, cooled, and filtered. The filtrate was passed through a column of Zeo-Karb 225 (previously washed successively with alkali, water, acid, and water) and washed through with distilled water until the eluate no longer left a residue on evaporation. 2N-Ammonia was then passed through the column until the eluate no longer gave a positive test with ninhydrin, and the collected ammoniacal extracts were then evaporated to a small volume and diluted with ethanol; the *amino-acid* (2·4 g.) separated as needles, m. p. 206—207° (decomp.) (Found: C, 63·45; H, 7·6; MeO, 12·4. $C_{11}H_{15}O_3N$ requires C, 63·15; H, 7·2; MeO, 14·8%). This (7·9 g.) was also obtained by direct hydrolysis of diethyl acetamido-o-(methoxymethyl)benzylmalonate (15 g.) with concentrated sulphuric acid (10 ml.) and water (170 ml.) for 48 hr.

The hydrolysis was also effected by heating the ester (1 g.) for 8 hr. on a water-bath with potassium hydroxide (2 g.) and water (2 ml.); acidification by acetic acid and evaporation (water-bath/reduced pressure) until the solution was neutral, gave the amino-acid (0·5 g.) after passage through a Zeo-Karb column.

A solution of the amino-acid (1·5 g.) in 2N-sodium hydroxide (5 ml.) was cooled in ice, with stirring, while 2N-sodium hydroxide (5 ml.) and acetic anhydride (0·5 ml.) were added. At intervals of 5 min. this addition of alkali followed by anhydride was repeated three times more. The mixture was kept at room temperature for 30 min., cooled in ice, and treated with 6N-sulphuric acid (9 ml.). The solid which separated had m. p. 158° and was identical with the *N*-acetyl-β-(*o*-methoxymethyl)phenylalanine above.

ω-*Ethoxy*-o-*toluic Acid*.—This was prepared as described for ω-methoxy-*o*-toluic acid by Clemo and Swan.[4] The ethyl ester formed needles, m. p. 22—23°, b. p. 165°/16 mm. (Found: C, 69·45; H, 8·05. Calc. for $C_{12}H_{16}O_3$: C, 69·25; H, 7·7%). The acid recrystallised from benzene–light petroleum, then sublimed at 70°/0·02 mm., forming needles, m. p. 82—83° (Found: C, 66·55; H, 6·75. Calc. for $C_{10}H_{12}O_3$: C, 66·65; H, 6·65%). Noyes and Coss,[16] using a different method of preparation, give b. p. 160°/20 mm. for the ester and m. p. 84—85° for the acid.

o-(*Ethoxymethyl*)*benzyl Alcohol*.—Reduction of the above ester, as described by Mann and Stewart [15] for the ω-methoxy-compound, gave the alcohol, b. p. 146—147°/18 mm. (Found: C, 72·6; H, 9·1. Calc. for $C_{10}H_{14}O_2$: C, 72·3; H, 8·45%). This gave a 3 : 5-*dinitrobenzoate*, m. p. 52° (from ethanol) (Found: C, 56·2; H, 4·5. $C_{17}H_{16}O_7N_2$ requires C, 56·65; H, 4·45%). The *chloride* was lachrymatory (b. p. 133—134°/20 mm.) (Found: C, 64·55; H, 6·9. $C_{10}H_{13}OCl$ requires C, 65·05; H, 7·05%).

*Attempted Reaction of* β-(o-*Methoxymethyl*)*phenylalanine with Formaldehyde*.—When the amino-acid was treated with formaldehyde and hydrochloric acid as described by Archer [17] for the preparation of 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid from β-phenylalanine, it yielded a small amount of viscous material, which was removed, and the filtrate was concentrated to half its volume and kept overnight in a refrigerator, giving crystals of 1 : 2 : 3 : 4-*tetrahydroisoquinoline-3-carboxylic acid hydrochloride*, m. p. 305° (decomp.) (Found: C, 56·2; H, 5·75. $C_{10}H_{11}O_2N$,HCl requires C, 56·2; H, 5·6%). Ammonia liberated the free amino-acid, m. p. 311—312°. With ethanol and concentrated sulphuric acid it gave the ester, b. p. 165° (bath-temp.)/2 mm. (Found: C, 70·75; H, 7·9. Calc. for $C_{12}H_{15}O_2N$: C, 70·25; H, 7·3%), which yielded a picrate, m. p. 195—196° (decomp.) (Found: C, 49·9; H, 4·05. Calc. for $C_{12}H_{15}O_2N,C_6H_3O_7N_3$: C, 49·75; H, 4·15%), and a *picrolonate*, m. p. 225° (decomp.) (Found: C, 56·0; H, 5·3. $C_{12}H_{15}O_2N,C_{10}H_8O_5N_4$ requires C, 56·3; H, 4·9%). Variation of the conditions gave the same product.

*Diethyl* o-(*Methoxymethyl*)*benzylmalonate*.—Diethyl malonate (14·4 g.), followed by *o*-(methoxymethyl)benzyl chloride (15 g.) during 20 min., was added with stirring to a cold solution of sodium (2·1 g.) in absolute ethanol (45 ml.). The mixture was refluxed for 6 hr., then filtered, and the filter cake was washed with hot ethanol. Distillation of the combined ethanolic solutions yielded the *ester* (23 g.), b. p. 220—250°/18 mm. (Found: C, 65·6; H, 7·7. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%).

[16] Noyes and Coss, *J. Amer. Chem. Soc.*, 1920, **42**, 1280.
[17] Archer, *J. Org. Chem.*, 1951, **16**, 430.

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β-(o-*Methoxymethyl*)*phenylpropionic Acid*.—The above ester (23 g.) was heated for 24 hr. on a water-bath with potassium hydroxide (23 g.) in water (23 ml.). The cooled solution was extracted with ether, acidified with concentrated hydrochloric acid, and extracted again with ether. The residue left after removal of the ether from the latter extract was heated for 30 min. at 160°. On cooling, the residue (14·4 g.) solidified, and recrystallisation from light petroleum (b. p. 60—80°) gave the *acid* as needles, m. p. 75—76°, unchanged by sublimation at 60°/0·01 mm. (Found: C, 68·3; H, 7·6. $C_{11}H_{14}O_3$ requires C, 68·05; H, 7·2%).

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UNIVERSITY OF DURHAM, KING'S COLLEGE,
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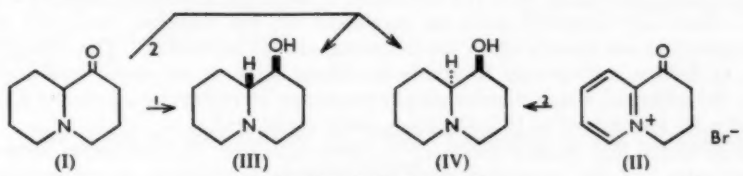
## NOTES.

### 414. *Stereoisomeric* 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*Octahydro*-1-*hydroxypyridocolines.*

By G. A. SWAN.

CLEMO and RAMAGE [1] reduced 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-1-oxopyridocoline (I) with sodium amalgam to 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydro-1-hydroxypyridocoline, m. p. 65—68°. In our hands this gave a product (III), m. p. 72°. 1 : 2 : 3 : 4-Tetrahydro-1-oxopyridocolinium bromide [2] (II) in acetic acid solution absorbed 4 mols. of hydrogen in the presence of Adams catalyst, giving the isomer (IV), m. p. 80°. Catalytic hydrogenation of the octahydro-ketone (I) gave a mixture of these alcohols.




(I) (III) (IV) (II)

1, Na–Hg. 2, $H_2$–Pt–AcOH.

The structures assigned rest on the following arguments: The more thermodynamically stable isomer (III), with the hydroxyl group equatorial, will be formed by sodium amalgam. Catalytic hydrogenation of the tetrahydro-ketone does not proceed *via* the octahydro-ketone since the former gives a single and the latter a mixed product. If then hydrogenation of the carbonyl group of (II) is the first step, the bridge-head hydrogen atom will enter on the opposite side of the rings to the hydroxyl group, leading to structure (IV). The keto-group of the octahydro-compound (I) is enolisable, so the hydrogenation product is a mixture.

*Experimental.—Reduction of* 1 : 2 : 3 : 4-*tetrahydro*-1-*oxopyridocolinium bromide* (II). The bromide (137 mg.) in acetic acid (10 ml.) absorbed 54·9 ml. of hydrogen at 18°/760 mm. during 40 min. in the presence of freshly reduced Adams catalyst (50 mg.) which was then removed immediately by filtration. The filtrate was evaporated to dryness (water-bath/reduced pressure). A solution of the residue in hot methanol was filtered and evaporated, giving a gum,

[1] Clemo and Ramage, *J.*, 1931, 437.
[2] Prasad and Swan, *J.*, 1958, 2024.

which was dissolved in a little hot acetone. Diluting the solution with ether gave a hydrobromide (90 mg.), m. p. 216° (from ethanol–acetone). When its solution in a little water was treated with 40% sodium hydroxide solution an oil separated, but soon solidified, giving 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydro*-1-*hydroxypyridocoline B* (IV), separating from light petroleum (b. p. 40—60°) as prisms, m. p. 80° (Found: C, 70·1; H, 11·1. $C_9H_{17}ON$ requires C, 69·65; H, 11·0%). This gave a *picrate*, prisms (from ethyl acetate), m. p. 152—153° (for analysis dried for 1 hr. at 90°/0·1 mm.) (Found: C, 46·35; H, 4·9. $C_9H_{17}ON,C_6H_3O_7N_3$ requires C, 46·75; H, 5·2%).

*Reduction of* 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydro*-1-*oxopyridocoline* (I). (*a*) Reduction with sodium amalgam was as described by Clemo and Ramage [1] and the distilled product yielded 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*octahydro*-1-*hydroxypyridocoline A hydrobromide*, prisms, m. p. 243—244° (from ethanol) (Found: C, 45·25; H, 7·95. $C_9H_{18}ONBr$ requires C, 45·75, H, 7·65%). Basification yielded *base A* (III), separating from light petroleum (b. p. 40—60°) as needles, m. p. 72° (Found: C, 69·7; H, 10·8%).

(*b*) The ketone (0·137 g.) in acetic acid absorbed 20·9 ml. of hydrogen at 18°/760 mm. during 35 min. in the presence of Adams catalyst (60 mg.). The resulting hydrobromide, on fractional crystallisation from ethanol, yielded the less soluble salt of base A, together with the more soluble *salt* of base B; the latter had m. p. 232—233° (from ethanol–acetone) (Found: C, 45·95; H, 7·9%) and yielded base B, prisms, m. p. 81° [from light petroleum (b. p. 40—60°)] (Found: C, 69·1; H, 10·65%).

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## 415. *The Depolymerisation of Paraldehyde in the Solvent System* $ZnCl_2$–$CH_3{\cdot}CO_2H$.

By D. P. N. SATCHELL.

IN the solvent system zinc chloride–acetic acid, the exchange of "aromatic" hydrogen shows the same parallelism with the ionisation of Brønsted indicator bases as it does in systems where only Brønsted acids are involved.[1] It was therefore concluded that the zinc chloride does not directly affect the ionisation of such indicators. The solvent system appears to behave analogously to the hydrochloric acid– or sulphuric acid–acetic acid systems, the addition of zinc chloride simply producing an increasing amount of a complex Brønsted acid, formulated as $H_2ZnCl_2(OAc)_2$, with acetic acid.

Because of the high acidity necessary to effect exchange, the correlation between the exchange rates and the ionisation data was necessarily observed at rather large zinc chloride concentrations. In order to demonstrate that this solvent system behaves like the conventional Brønsted acidic systems at low zinc chloride concentrations also, we must study another reaction whose rate runs parallel with indicator ionisation in the presence of Brønsted acids, but which proceeds measurably at low acidities. Such a reaction is the depolymerisation of paraldehyde,[2] one of particular interest in connection with this type of solvent system in that it is catalysed by both Lewis and Brønsted acids.[3] Some free zinc chloride will doubtless be in equilibrium with $H_2ZnCl_2(OAc)_2$ (though the quantity may be very small) and therefore if the behaviour of the zinc chloride–acetic acid system at low zinc chloride concentrations *is* similar to that at higher concentrations, the depolymerisation rates would be expected either to run parallel with the indicator ionisation data or to increase somewhat faster. The latter circumstance would arise if the free zinc chloride appreciably catalysed the depolymerisation.

The rate of depolymerization for stoicheiometric zinc chloride concentrations between 0·016M and 0·212M at 25° was studied; the indicator ionisation data for this composition

[1] Satchell, *J.*, 1927.
[2] Bell and Brown, *J.*, 1954, 774; Satchell, *J.*, 1957, 3524.
[3] Bell and Skinner, *J.*, 1952, 2955.

range for *o*-nitroaniline have been given previously.[4] The Table contains the values of the first-order depolymerisation rate constants ($k$), together with the appropriate values of the logarithm of the indicator ionisation ratio ($I$). If log $k$ is plotted against log $I$ a good

*Depolymerisation of paraldehyde in the zinc chloride–acetic acid solvent system at 25°.*

| | | | | | | |
|---|---|---|---|---|---|---|
| $ZnCl_2$ (M) | 0·016 | 0·027 | 0·053 | 0·106 | 0·159 | 0·212 |
| $-\log I$ | 2·07 | 1·83 | 1·49 | 1·08 | 0·80 | 0·56 |
| $10^4k$ (sec.$^{-1}$) | 0·46 | 0·86 | 2·20 | 6·51 | 14·0 | 29·9 |

straight line of slope 1·15 is obtained. The observed correlation between rates and ionisation is thus, as for the exchange reactions at higher zinc chloride concentrations, of the kind found in systems containing only Brønsted acids. The value of the slope is also very similar to that found in such systems.[2] Hence it seems very likely (*a*) that at low, as well as high, zinc chloride concentrations, the addition of this compound to anhydrous acetic acid produces an acidic system which behaves analogously to systems such as hydrochloric–acetic acid, from the viewpoints of both ionisation equilibria and acid catalysis, and (*b*) that free zinc chloride plays no significant part in the depolymerisation of paraldehyde in the zinc chloride–acetic acid system. This may be because its concentration is very low and/or because its catalytic power is small compared with that possessed by the medium due to its Brønsted acidity.

*Experimental.—Materials.* These were prepared as previously described.[3,5]

*Depolymerisation rates.* The titration method[3] was found suitable. The paraldehyde concentration was *ca.* 0·03M, and " infinity " titres showed the reaction to proceed to *ca.* 97% completion. The rate of depolymerisation was studied at six different zinc chloride concentrations, and in all cases the first-order plot was linear over at least the first 70% of reaction. The rate constants were reproducible to ±5%.

Fresh and aged zinc chloride–acetic acid mixtures possessed the same catalytic power. Hence there is no slow reaction occurring in the solvent system itself which affects its acidic properties.

KING'S COLLEGE, STRAND, LONDON, W.C.2. [*Received, November 7th,* 1957.]

[4] Bethell, Gold, and Satchell, *J.*, 1918.
[5] Satchell, *J.*, 1916.

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## 416. *The Heat of Formation of Nickel Carbonyl from Combustion Calorimetry.*

By K. W. SYKES.

THE apparent difference[1] of 8 kcal. mole$^{-1}$ between the two most recent calorimetric measurements of the heat of formation of nickel carbonyl is largely due to discrepancies in the interpretation of the results. Fischer, Cotton, and Wilkinson[1] assumed that Smagina and Ormont's result[2] for liquid carbonyl (47·3 kcal. mole$^{-1}$) referred to gaseous carbonyl, while the latter authors used different auxiliary data of unspecified origin. Smagina and Ormont[2] took the heat of combustion of 4 moles of carbon monoxide at constant volume at 25° C to be 270·5 kcal., which is the figure given by standard tables[3] for constant pressure; it should be replaced by $-\Delta E = -\Delta H - 2RT = 269{\cdot}3$ kcal. They also assumed that the heat of combustion of one mole of nickel at constant volume at 25° was 58·9 kcal., whereas a more recent value[4] which Fischer, Cotton, and Wilkinson

[1] Fischer, Cotton, and Wilkinson, *J. Amer. Chem. Soc.*, 1957, **79**, 2044.
[2] Smagina and Ormont, *J. Gen. Chem. U.S.S.R.*, 1955, **25**, 207 (English translation by Consultants Bureau, Inc., New York).
[3] " Selected Values of Chemical Thermodynamic Properties," Nat. Bur. Standards. Circular 500, Washington, 1952.
[4] Boyle, King, and Conway, *J. Amer. Chem. Soc.*, 1954, **76**, 3835.

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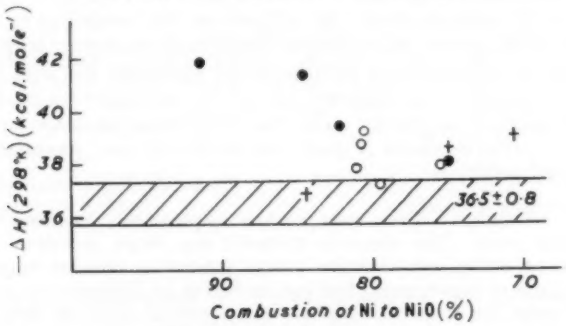
used gives $-\Delta E = -\Delta H - \frac{1}{2}RT = 57{\cdot}0$ kcal. With these corrections and a heat of vaporisation of 6·5 kcal. mole$^{-1}$,[1,5] Smagina and Ormont's three results for the heat of formation of gaseous carbonyl become $-\Delta H$ (298° K) = (i) 36·9, (ii) 39·0, (iii) 38·6 kcal. mole$^{-1}$, as compared with Fischer, Cotton, and Wilkinson's estimate of 39·1 kcal. mole$^{-1}$.

The individual values of $-\Delta H$ (298° K), calculated as above for gaseous carbonyl, vary systematically over a range of several kcal. mole$^{-1}$ with the percentage combustion of nickel to nickel oxide (Figure), but this variation runs in different directions in the two investigations. No appreciable trend is to be expected because the heat of combustion of nickel powder is constant to within 0·05 kcal. mole$^{-1}$ over the range 87—93% combustion.[4]

*Heat of formation of gaseous nickel carbonyl.*




Fischer, Cotton, and Wilkinson [1]: ● internal ignition; ○ external ignition.
Smagina and Ormont [2]: +
Sykes and Townshend [6] (from equilibrium constant): shaded band.

The spread of the experimental values is thus probably due to errors in the measurement of the percentage combustion, a 1% deviation in which affects $\Delta H$ by 0·6 kcal. mole$^{-1}$. Fischer, Cotton, and Wilkinson's distinction between runs with external and internal ignition, attributed to hydration or further oxidation of nickel oxide in the former, does not appear to be valid since the results agree when the percentage combustion is the same. All the points in the Figure give a mean and standard deviation of 38·8 $\pm$ 1·5 kcal. mole$^{-1}$, which is the best estimate to be derived from the calorimetric data. In view of the uncertainties involved, the agreement with the figure of 36·5 $\pm$ 0·8 kcal. mole$^{-1}$ calculated by Sykes and Townshend [6] from the equilibrium constant is as close as can be expected.* It now seems unlikely that the true value lies outside the range 36—40 kcal. mole$^{-1}$, but greater precision could only be obtained by more accurate experiments.

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[*Received, December 10th*, 1957.]

* Fischer, Cotton, and Wilkinson misquote this value in their Table III, but are correct in stating that Sykes and Townshend omitted from the denominator of the expression for $C$ a factor 4 which is necessary and which was included in the calculation.

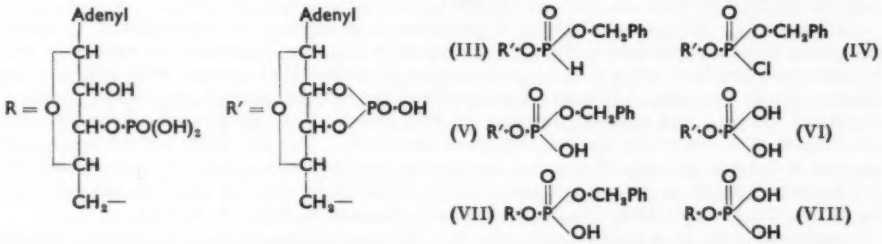
[5] Spice, Staveley, and Harrow, *J.*, 1955, 100.
[6] Sykes and Townshend, *J.*, 1955, 2528.

## 417. *An Alternative Synthesis of Adenosine-2′(3′) : 5′ Diphosphate.*

By A. M. Michelson.

Todd and his co-workers [1] have described the synthesis of a mixture of adenosine-2′ : 5′ and -3′ : 5′ diphosphate wherein adenosine is phosphorylated directly with dibenzyl phosphorochloridate and the benzyl groups are later removed. An alternative synthesis from adenosine-2′(3′) phosphate has been developed: while the overall yield is not high, some of the intermediates are of possible use for the synthesis of certain co-enzymes.

A solution of the anhydrous mono(tri-*n*-decylamine) salt of adenosine-2′(3′) phosphate (I) (commercial yeast adenylic acid) in dioxan was treated with diphenyl phosphorochloridate,[2] giving adenosine-2′ : 3′ cyclic phosphate (II) quantitatively.[3] This with




*O*-benzylphosphorous di-*O*-phenylphosphoric anhydride [4] gave a 50% yield of adenosine 2′ : 3′-(cyclic phosphate) 5′-(benzyl phosphite) (III) which was separated from the concomitant polymers.[5] Treatment of the crude phosphite in the usual way [6] with *N*-chlorosuccinimide gave the phosphorochloridate (IV), which with aqueous lutidine yielded an intermediate, presumably adenosine 2′ : 3′-(cyclic phosphate) 5′-(benzyl phosphate) (V). Hydrogenation then gave adenosine 2′ : 3′-(cyclic phosphate) 5′-phosphate (VI), converted by alkali into a mixture of the 2′ : 5′- and the 3′ : 5′-diphosphate (VIII) of adenosine. Alternatively, treatment of adenosine 2′ : 3′-(cyclic phosphate) 5′-(benzyl phosphate) with alkali produced the 2′(3′)-phosphate 5′-(benzyl phosphate) (VII) which was readily hydrogenated to adenosine-2′(3′) : 5′ diphosphate.

*Experimental.—Adenosine 2′ : 3′-(cyclic phosphate) 5′-(benzyl phosphite).* Diphenyl phosphorochloridate (1·56 c.c.) was added to a solution of mono(tri-*n*-decylammonium)adenosine-2′(3′) phosphate (from 2 g. fo the nucleotide) in dry dioxan (20 c.c.), and the solution left at room temperature for 1 hr. with occasional shaking. *O*-Benzylphosphorous di-*O*-phenylphosphoric anhydride (from 3 g. of benzyl dihydrogen phosphite [4]) in dioxan (20 c.c.) was then added, followed dropwise by a solution of 2 : 6-lutidine (1·85 g.) in dioxan (5 c.c.) with stirring under anhydrous conditions. The clear solution was set aside at room temperature overnight. Solvent was removed under reduced pressure and a mixture of ether (50 c.c.) and *cyclo*hexane (50 c.c.) added to the residue with vigorous shaking. The precipitated solids were dissolved in a little dioxan, tri-*n*-butylamine being added to neutrality. Methyl cyanide (50 c.c.) was then added and the precipitated polymer material [5] centrifuged off. The supernatant liquids were concentrated to small volume, dry benzene (50 c.c.) was added, and the resultant precipitate of phosphate phosphite washed with small quantities of ether and dried to a white solid foam (1·975 g.). Although analyses were unsatisfactory, possibly owing to the indeterminate amount

[1] Cramer, Kenner, Hughes, and Todd, *J.*, 1957, 3297.
[2] Brigl and Müller, *Ber.*, 1939, **72**, 2121.
[3] Michelson, *Chem. and Ind.*, 1958, 70.
[4] Corby, Kenner, and Todd, *J.*, 1952, 3669.
[5] Michelson, unpublished work.
[6] Kenner, Todd, and Weymouth, *J.*, 1952, 3675.

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of base held by the compound, the material was almost homogeneous, running as a single spot in paper chromatography, free from other nucleotide and phosphorus compounds.

*Adenosine 2′(3′)-phosphate 5′-(benzyl phosphate).* The above phosphate phosphite (0·478 g.) in methyl cyanide (2·5 c.c.) and dioxan (2·5 c.c.), with sufficient tri-*n*-butylamine to ensure solution, was added to *N*-chlorosuccinimide (0·15 g.). After 1 hr. at room temperature aqueous N-lithium hydroxide (5 c.c.) was added, the mixture left at room temperature overnight, neutralised with N-hydrochloric acid, and evaporated under reduced pressure, and alcohol (10 c.c.) was added to the residue. A trace of water was added to dissolve precipitated matter, followed by ethanolic calcium chloride (250 mg. in 25 c.c.). The precipitated *calcium salt* of adenosine 2′(3′)-phosphate 5′-(benzyl phosphate) was centrifuged off, washed with alcohol, and ether, and dried (0·414 g.) [Found, in material dried at 50°/$10^{-3}$ mm. for 12 hr.: P, 10·6. $(C_{17}H_{18}O_{10}N_5P_2)_2Ca_2$ requires P, 10·8%].

*Adenosine-2′(3′) : 5′ diphosphate.* Hydrogenation of the preceding ester in water with a palladium catalyst at atmospheric pressure gave a mixture of adenosine 2′ : 5- and 3′ : 5′-diphosphate, isolated as the calcium salt in the usual way (Found, in material dried at 50°/$10^{-3}$ mm. for 12 hr.: N, 13·5; P, 12·6. Calc. for $C_{10}H_{11}O_{10}N_5P_2Ca_2$: N, 13·9; P, 12·3%).

*Adenosine 2′ : 3′-(cyclic phosphate) 5′-phosphate.* A solution of adenosine 2′ : 3′-cyclic phosphate 5′-(benzyl phosphite) (0·63 g.) in dioxan (8 c.c.) was treated in the usual way with *N*-chlorosuccinimide (0·198 g.), and the crude phosphorochloridate treated with 50% aqueous lutidine (5 c.c.) overnight. Solvent was removed under reduced pressure, the residue dissolved in ethanol (15 c.c.), and ethanolic calcium chloride added. The precipitated calcium salt was centrifuged off, washed with alcohol, and ether, and dried. This fine white powder was hydrogenated in water in the normal way and the resultant *calcium adenosine 2′ : 3′-(cyclic phosphate) 5′-phosphate* isolated as its calcium salt (0·31 g.) [Found, in material dried at 50°/$10^{-3}$ mm. for 12 hr.: N, 14·6; P, 13·4. $(C_{10}H_{10}O_9N_5P_2)_2Ca_2$ requires N, 15·0; P, 13·3%].

Treatment with 0·1 N-sodium hydroxide at room temperature gave a mixture of adenosine-2′ : 5′ and -3′ : 5′ diphosphate.

*Paper chromatography.* $R_P$ values, for ascending chromatograms on Whatman No. 1 paper with 95% ethanol–M-ammonium acetate (75 : 30) as the solvent, were: adenosine 0·58; (II) 0·49; (III) 0·62; (V) 0·45; (VII) 0·24; (I) 0·15; adenosine-5′ phosphate 0·13; (VI) 0·09; (VIII) 0·02; adenosine-5′ pyrophosphate 0·05.

*Paper electrophoresis.* Movements towards the anode on Whatman No. 1 paper, 30 cm. in length, (*a*) in M/50-$KH_2PO_4$ at 500 v for 60 minutes, and (*b*) in M/50-$Na_2HPO_4$ at 400 v for 90 min., respectively are: (I) 5·5, 9·2; (II) 5·3, 5·8; (V) 7·6, 9·3; (VII) 8·3, 11·3; (VI) 8·8, 11·4; (VIII) 8·8, 12·5; adenosine-5′ pyrophosphate 7·0, 9·2.

Thanks are offered to Dr. A. K. Mills for interest and encouragement and to the directors of Arthur Guinness Son & Co. (Dublin) Ltd. for permission to publish this work.

ARTHUR GUINNESS SON & CO. (DUBLIN) LTD.,
DUBLIN, EIRE.

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## 418. *Properties and Reactions of Free Alkyl Radicals in Solution. Part X.* Further Studies of Tertiary Hydroxylamines.*

By A. N. BOYD, P. F. SOUTHERN, and WILLIAM A. WATERS.

THE preparation of tri-(2-cyano-2-propyl)hydroxylamine from nitric oxide and 2-cyano-2-propyl radicals was described in Part VII.[1] We have now extended this work and have established that the addition of 2-methoxycarbonyl-2-propyl radicals to nitric oxide occurs in stages, for the intermediate methyl α-nitroso*iso*butyrate can be removed by distillation and converted with nitrogen dioxide (as in Part IX [2]) into methyl α-nitro-*iso*butyrate.

Alkaline hydrolysis of *ON*-di-(2-methoxycarbonyl-2-propyl)-*N*-phenylhydroxylamine

* Part IX, *J.*, 1957, 3129.

[1] Gingras and Waters, *J.*, 1954, 1920.
[2] Tilney-Bassett and Waters, *J.*, 1957, 3129.

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yields the corresponding dibasic acid which is easily converted into a stable anhydride that must contain a seven-membered ring. Bouveault–Blanc reduction of the above ester gives aniline and α-hydroxy*iso*butyric acid whilst reduction with lithium aluminium hydride yields *ON*-di-(2-hydroxy-1 : 1-dimethylethyl)-*N*-phenylhydroxylamine. Boiling 2N-hydrochloric acid decomposes the latter, giving some *iso*butyraldehyde and a basic residue which, after benzoylation yields some benzanilide and a small amount of a product that appears to be *N*-(2-benzoyloxy-1 : 1-dimethylethyl)-*p*-chloroaniline. The mechanism of formation of *p*-chloroaniline from *N*-phenylhydroxylamine [3] serves to indicate how the latter could have been formed: aldehydes have previously been reported as products of acid hydrolysis of tertiary hydroxylamines.[4]

## Experimental

ONN-(*Tri*-1-*cyano*cyclo*hexyl*)*hydroxylamine*.—After air had been displaced with nitrogen, nitric oxide was passed slowly for 7 hr. through a refluxing solution of 1 : 1′-azobis-1-cyano-*cyclo*hexane (9 g.) in dry toluene (100 ml.). The toluene was removed and the product, in light petroleum–benzene, was separated through alumina into 1 : 1′-dicyanodi*cyclo*hexyl (1·1 g.; m. p. 222°) and ONN-*tri*-(1-*cyano*cyclo*hexyl*)*hydroxylamine* (4·6 g.), m. p. 144° (from methanol) (Found: C, 71·0; H, 8·5; N, 16·1. $C_{21}H_{36}ON_4$ requires C, 71·1; H, 8·5; N, 15·8%). Hydrolysis with dilute sodium hydroxide solution yielded a little *cyclo*hexanone (dinitrophenylhydrazone, m. p. and mixed m. p. 154°); cold concentrated hydrochloric acid did not effect hydrolysis.

ONN-*Tri*-(2-*methoxycarbonyl*-2-*propyl*)*hydroxylamine*.—Nitric oxide diluted with nitrogen was passed slowly for 6 hr. into a refluxing solution of dimethyl αα′-azo*iso*butyrate (13·8 g.) in dry benzene (150 ml.). After the solution had been flushed with nitrogen the benzene was removed under diminished pressure, and the residue in a little light petroleum (b. p. under 40°) was cooled (methanol–solid carbon dioxide) until it crystallised. Recrystallisation gave ONN-*tri*-(2-*methoxycarbonyl*-2-*propyl*)*hydroxylamine*, m. p. 55°, additional material being obtained by chromatographic separation of mother liquors that contained also dimethyl tetramethylsuccinate (total yield 5·9 g., 44%) (Found: C, 54·5; H, 8·1; N, 3·9. $C_{15}H_{27}O_7N$ requires C, 54·0; H, 8·2; N, 4·2%). In a similar experiment with less solvent volatile materials were distilled away as the reaction proceeded whilst fresh benzene was added dropwise at a corresponding rate. The green distillate was warmed with nitrogen dioxide, benzene was removed, and the residue was distilled giving methyl α-nitro*iso*butyrate (2 g.), b. p. 85—95°/19 mm., which was identified, after crystallisation at low temperature, by its refractive index and infrared spectrum.[2]

Alkaline hydrolysis of *ONN*-tri-(2-methoxycarbonyl-2-propyl)hydroxylamine caused extensive decomposition. Reduction in ether with lithium aluminium hydride gave ONN-*tri*-(2-*hydroxy*-1 : 1-*dimethylethyl*)*hydroxylamine* (72%), needles, m. p. 74° [from light petroleum (b. p. 60—80°)] (Found: C, 58·0; H, 10·7; N, 5·3. $C_{12}H_{27}O_4N$ requires C, 57·8; H, 10·9; N, 5·6%). This was basic enough to dissolve in dilute mineral acid.

ON-*Di*-(2-*methoxycarbonyl*-2-*propyl*)-N-*phenylhydroxylamine*.—Prepared from nitrosobenzene and dimethyl αα′-azo*iso*butyrate in boiling toluene (compare Part VII) in 66% yield, this *hydroxylamine* had m. p. 69° [from light petroleum (b. p. 40—60°)] (Found: C, 62·0; H, 7·6; N, 4·5. $C_{16}H_{23}O_5N$ requires C, 62·1; H, 7·4; N, 4·5%). Reaction in benzene gave a much lower yield whilst use of boiling xylene led to decomposition of the nitrosobenzene. The isomeric chloronitrosobenzenes decomposed too quickly in boiling toluene for effective reaction with 2-methoxycarbonyl-2-propyl free radicals: small amounts of nitro- and azoxy-compounds were isolated. Alkaline hydrolysis of the above ester in aqueous alcohol yielded ON-*di*-(2-*carboxy*-2-*propyl*)-N-*phenylhydroxylamine* which had m. p. 154° (decomp.) when heated rapidly, but when slowly heated decomposed at 129—130° (Found: C, 59·8; H, 6·9; N, 4·9. $C_{14}H_{19}O_5N$ requires C, 59·7; H, 6·8; N, 5·0%). It evolved carbon monoxide when heated with concentrated sulphuric acid. With boiling acetic anhydride it yielded the *cyclic anhydride*, m. p. 135° (from methanol) (Found: C, 63·9; H, 6·5; N, 5·25. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%). The infrared spectrum of this was typical of acid anhydrides, with absorption bands

[3] Hughes and Ingold, *Quart. Rev.*, 1952, **6**, 34.
[4] Jones and Major, *J. Amer. Chem. Soc.*, 1928, **50**, 2742; Kleinschmidt and Cope, *ibid.*, 1944, **66**, 1929; Meisenheimer, *Ber.*, 1919, **52**, 1667.

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at 1760 and 1800 cm.$^{-1}$. The anhydride, which was easily hydrolysed to the original acid by treatment with aqueous sodium hydroxide, condensed with resorcinol to an alkali-soluble product having a green fluorescence. A *monoamide*, m. p. 141°, of *ON*-di-(2-carboxy-2-propyl)-*N*-phenylhydroxylamine was obtained by treating the anhydride in dioxan with ammonia (Found: C, 59·6; H, 7·2; N, 10·1. $C_{14}H_{20}O_4N_2$ requires C, 60·0; H, 7·2; N, 10·0%). Hydrolysis of *ON*-di-(2-cyano-2-propyl)-*N*-phenylhydroxylamine with 6% sodium hydroxide in aqueous alcohol gave a cyano-amide, m. p. 220—221° (decomp.) (Found: C, 64·6; H, 7·5; N, 15·9. $C_{14}H_{19}O_2N_3$ requires C, 64·3; H, 7·3; N, 16·1%), whose infrared spectrum showed absorption due to the carbamoyl but not that due to the cyano-group. Since the latter absorption is often suppressed in nitriles having strongly polar α-substituents [2] the substance is probably N-(*2-carbamoyl-2-propyl*)-O-(*2-cyano-2-propyl*)-N-*phenylhydroxylamine*.

Reduction of *ON*-di-(2-methoxycarbonyl-2-propyl)-*N*-phenylhydroxylamine (2·1 g.) with sodium metal (8 g.) and ethanol (50 ml.) gave an alkaline solution from which a little aniline could be extracted. Acidification yielded, besides *ON*-di-(2-carboxy-2-propyl)-*N*-phenylhydroxylamine, α-hydroxy*iso*butyric acid (20 mg.), m. p. 77°, unchanged after admixture with an authentic specimen prepared as described by Hepworth.[5] Reduction of the above ester (3 g.) with lithium aluminium hydride (0·75 g.) in ether (50 ml.) followed by treatment with alkali to dissolve alumina gave the basic product ON-*di*-(*2-hydroxy*-1 : 1-*dimethylethyl*)-N-*phenylhydroxylamine* (2 g.), m. p. 69° (from light petroleum) (Found: C, 66·2; H, 9·1; N, 5·5. $C_{14}H_{23}O_2N$ requires C, 66·4; H, 9·2; N, 5·5%) [*diphenylurethane*, m. p. 130° (Found: C, 68·7; H, 7·0; N, 8·1. $C_{28}H_{33}O_5N_3$ requires C, 68·4; H, 6·8; N, 8·5%)]. Hydrolysis of this hydroxy-compound (2 g.) with boiling 2N-hydrochloric acid under nitrogen gave a little *iso*butyraldehyde (dinitrophenylhydrazone, m. p. 178°, mixed m. p. 180°) and, after benzoylation, benzanilide (0·19 g.), and a product (0·49 g.), m. p. 72°, which, from its infrared spectrum, appears to be N-(*2-benzoyloxy*-1 : 1-*dimethylethyl*)-p-*chloroaniline* (Found: C, 67·8; H, 6·3; N, 4·8; Cl, 11·5. $C_{17}H_{18}O_2NCl$ requires C, 67·2; H, 6·0; N, 4·6; Cl, 11·7%). The infrared spectrum had peaks at 2·96 μ (NH), 5·86, 7·78, and 8·95 μ (Ph·CO·O), 7·18 and 7·29 μ ($CMe_2$), and 12·30 μ (*para*-substituted phenyl).

All the trisubstituted hydroxylamines described show distinct infrared absorptions in the same 8 wave-bands listed in Part VII, *i.e.*, 7·6—7·9 μ; 8·25—8·5 μ, 2 or 3 bands; 8·6—8·7 μ; 9·35 μ; 9·5—9·95 μ, 2 bands; 10·1 and 10·3—10·4 μ; 10·8—10·9 μ; and 11·1—11·9 μ, 2 bands.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, December 23rd*, 1957.]

[5] Hepworth, *J.*, 1919, 1207.

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## 419. *Some New Sulphur-containing Diacids.*

By W. A. W. CUMMINGS.

SINCE the literature contains few examples of the use of sulphur-containing acids in polyamides,[1] a number of acids of the following types have been used as monomers. Some of these compounds and their derivatives are new, and their synthesis is described.

(I) $HO_2C{\cdot}[CH_2]_x{\cdot}S{\cdot}[CH_2]_y{\cdot}S{\cdot}[CH_2]_x{\cdot}CO_2H$ $HO_2C{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_4(p){\cdot}S{\cdot}CH_2{\cdot}CO_2H$ (II)

$HO_2C{\cdot}[CH_2]_x{\cdot}C_6H_4(p){\cdot}S{\cdot}[CH_2]_y{\cdot}S{\cdot}C_6H_4(p){\cdot}[CH_2]_x{\cdot}CO_2H$ (III)

Four known examples of series (I) were prepared: $x = 1$, $y = 1$ (ref. 2); $x = 1$, $y = 2$ (ref. 3); $x = 1$, $y = 3$ (ref. 4); $x = 2$, $y = 3$ (ref. 5). All except the third were oxidised by hydrogen peroxide in acetic acid to the disulphones, this method being better than the permanganate oxidation used by Tiberg [7] for one case. The sulphones which contain the $\cdot SO_2{\cdot}CH_2{\cdot}CO_2H$ group are decarboxylated above 200°.

[1] B.P. 571,708; 670,177.
[2] Holmberg and Mattison, *Annalen*, 1907, **353**, 123.
[3] Ramberg and Tiberg, *Ber.*, 1914, **47**, 730.
[4] Rothstein, *Ber.*, 1925, **58**, 53.
[5] Larsson, Hernäss, and Torssell, *Trans. Chalmers Univ. Technol. Gothenburg, Sweden*, 1945, **47**, 13.
[6] Reuterskiöld, *Chem. Abs.*, 1940, **34**, 2791.
[7] Tiberg, *Ber.*, 1916, **49**, 2024.

β-(*p*-Carboxymethylthiophenyl)propionic acid (II) was prepared by the following route:

$$p\text{-}NH_2\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CO_2H \longrightarrow \underset{(IV)}{HS\cdot C_6H_4\cdot CH_2\cdot CH_2\cdot CO_2H} \longrightarrow (II)$$

β-*p*-Nitrophenylpropionic acid was prepared by Manske and Kulka's method [8] and on catalytic reduction gave the amino-acid. Treatment of the diazonium solution with potassium ethyl xanthate and decomposition with potassium hydroxide then gave the thiol-acid (IV), which with chloroacetic acid gave acid (II) in 44% overall yield from the amino-acid.

Two acids of series (III) were prepared: 1 : 3-di-(-*p*-carboxyphenylthio)propane (III; $x = 0$, $y = 3$) was made from *p*-mercaptobenzoic acid [9] and trimethylene dibromide, and 1 : 3-di-(*p*-2-carboxyethylphenylthio)propane (III; $x = 2$, $y = 3$) similarly from the acid (IV).

Some of these compounds gave fibre-forming polymers with hexamethylenediamine but none had useful textile properties.

*Experimental.—Methylenebis-sulphonylacetic acid.* Methylenebisthioglycollic acid [2] (10 g.), acetic acid (200 ml.), and 30% hydrogen peroxide (60 ml.) were heated under reflux for 3 hr. at 70°. The solution was concentrated to about 60 ml. and cooled. The precipitate recrystallised from ethyl acetate–benzene, giving *methylenebis-sulphonylacetic acid* (10·5 g., 40%), m. p. 209—210° (decomp.) (Found: C, 22·7; H, 2·9%; equiv., 131. $C_5H_8O_8S_2$ requires C, 23·1; H, 3·1%; equiv., 130) [*diethyl ester*, needles (from ethanol), m. p. 72—74° (Found: C, 34·6; H, 5·2; S, 20·3. $C_9H_{16}O_8S_2$ requires C, 34·2; H, 5·1; S, 20·4%)].

Ethylenebis-sulphonylacetic acid, similarly prepared (75% yield) from ethylenebisthioglycollic acid,[3] crystallised from water as plates, m. p. 230—232° (lit.,[6] 228—230°) (Found: equiv., 139. Calc. for $C_6H_{10}O_8S_2$: equiv., 137), and gave a diethyl ester, m. p. 80—81° (lit.,[7] 81°).

The acid (I; $x = 2$, $y = 3$) (5·5 g.), acetic acid (50 ml.), and 30% hydrogen peroxide (17 ml.) were heated for 1 hr. at 100°. The product which separated was recrystallised from water, giving 1 : 3-*di*-(2-*carboxyethylsulphonyl*)*propane* (6·65 g., 96%) as plates, m. p. 247—250° (decomp.) (Found: C, 34·4; H, 5·1. $C_9H_{16}O_8S_2$ requires C, 34·2; H, 5·1%) [*dimethyl ester*, plates (from acetone), m. p. 159·5—160° (Found: C, 38·25; H, 5·6; S, 18·35. $C_{11}H_{20}O_8S_2$ requires C, 38·4; H, 5·8; S, 18·6%)].

β-p-*Aminophenylpropionic acid.* β-*p*-Nitrophenylpropionic acid [8] (82 g.), alcohol (500 ml.), and 10% palladised charcoal (20 g.) were shaken with hydrogen until no further absorption occurred. After removal of the catalyst and excess of solvent the amino-acid, m. p. 130—131° (lit.,[8] 131—132°), crystallised.

β-p-*Mercaptophenylpropionic acid* (IV). The diazonium solution from the above amino-acid (69 g.), concentrated hydrochloric acid (89 ml.), water (160 ml.), and ice (400 g.), with sodium nitrite (33 g.) in water (80 ml.), was poured into a solution of potassium ethyl xanthate (140 g.) and sodium acetate (57 g.) in water (270 ml.). The yellow precipitate decomposed on a steam-bath. The resulting brown oil was extracted with ether and after removal of solvent was heated with potassium hydroxide (56 g.), water (50 ml.), and ethanol (300 ml.) in a stream of nitrogen. The solvent was removed and the mixture acidified with 10% sulphuric acid, giving a yellow oil which rapidly solidified. This was dissolved in ammonium carbonate solution, and filtered from small amounts of sulphur, and the mercapto-acid (35 g., 58%), m. p. *ca.* 100—105°, was reprecipitated with dilute sulphuric acid.

β-(p-*Carboxymethylthiophenyl*)*propionic acid* (II). The acid (IV) (20·7 g.), chloroacetic acid (10·5 g.), sodium dithionite (5 g.), and ethanol (150 ml.) were warmed together on the steam-bath. Sodium hydroxide (13·5 g.) in water (40 ml.) was added and the mixture heated under reflux for 4 hr. The product was filtered off and dissolved in warm water (charcoal), and the solution acidified with hydrochloric acid. The precipitate (20·9 g., 76%) recrystallised from ethanol, giving the *acid*, m. p. 203—205° (Found: C, 55·0; H, 4·7; S, 13·2%; equiv., 120. $C_{11}H_{12}O_4S$ requires C, 55·0; H, 5·0; S, 13·3%; equiv., 120). Its *hexamethylenediammonium salt* formed needles, m. p. 215—217° (decomp.) (Found: C, 57·4; H, 8·2; N, 7·9; S, 9·3%;

[8] Manske and Kulka, *Canad. J. Res.*, 1947, **25**, *B*, 376.
[9] Thompson, *J. Soc. Chem. Ind.*, 1925, **44**, 196T.

amine equiv., 183; carboxyl equiv., 179. $C_{11}H_{12}O_4S,C_6H_{14}N_2$ requires C, 57·3; H, 7·9; N, 7·9; S, 9·0%; amine and carboxyl equiv., 178).

p-*Mercaptobenzoic acid.* Diazotised *p*-aminobenzoic acid was converted into the thiol-acid (52%), m. p. 216—218° (lit.,[9] 219°), by the method described for β-*p*-aminophenylpropionic acid.

1 : 3-*Di*-(p-*carboxyphenylthio*)*propane.* *p*-Mercaptobenzoic acid (50 g.), sodium hydroxide (53 g.), sodium dithionite (15 g.), water (220 ml.), and absolute ethanol (320 ml.) were heated under reflux on a steam-bath. Trimethylene dibromide (29 ml.) was added during 12 min. and heating continued for 16 hr. Ethanol was removed, the residue dissolved in sodium carbonate solution (charcoal), and the solution acidified. The product was recrystallised 4 times from acetic acid, giving the *acid* (7·2 g., 13%), m. p. 256—258° (Found: C, 58·4; H, 5·0; S, 17·9. $C_{17}H_{16}O_4S_2$ requires C, 58·6; H, 4·6; S, 18·4%).

1 : 3-*Di*-(p-2′-*carboxyethylphenylthio*)*propane.* This was prepared in a similar manner from the acid (IV) (20 g.), sodium dithionite (5 g.), water (150 ml.), ethanol (200 ml.), and sodium hydroxide (14 g.). Trimethylene dibromide (12 ml.) was added during 4 hr., and heating continued overnight. Three recrystallisations of the product from acetic acid gave the *acid* (5 g., 22%), m. p. 143—144° (Found: C, 62·1; H, 5·8; S, 15·6. $C_{21}H_{24}O_4S_2$ requires C, 62·4; H, 5·9; S, 15·8%).

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RESEARCH DEPARTMENT, BRITISH NYLON SPINNERS LTD.,
PONTYPOOL, MONMOUTHSHIRE. [*Received, December* 23*rd*, 1957.]

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## 420. *Some Derivatives of* iso*Pentylbenzene.*

By W. E. HARVEY.

WE have prepared several derivatives of *iso*pentylbenzene, which are either new or have been obtained by routes superior to those previously described.

*iso*Pentylbenzene was most conveniently prepared from α-*iso*butylbenzyl alcohol which was smoothly dehydrated to β-*iso*propylstyrene by treatment with boiling 33% sulphuric acid (w/w), although more dilute acid was ineffective and more concentrated acid led to an excessive amount of polymer. Hydrogenation of β-*iso*propylstyrene gave very pure *iso*pentylbenzene in good yield.

Nitration of *iso*pentylbenzene gave approximately equal amounts of the *ortho*- and *para*-nitro-compounds which were converted into the corresponding bromo-compounds, amines, and carboxylic acids by standard methods. Nitration of *o*-*iso*pentylaniline [1] in concentrated sulphuric acid gave 5-nitro-2-*iso*pentylaniline whose structure follows from its method of preparation and its conversion into 2 : 4-diacetamido*iso*pentylbenzene.[2,3] Attempts to convert the nitro-amine into the corresponding nitro-nitrile by the Sandmeyer method with either copper or nickel [4] salts yielded only intractable gums.

*Experimental.*—Amides, anilides, and *p*-bromophenacyl esters were prepared by standard methods and crystallised from aqueous ethanol.

iso*Pentylbenzene.* α-*iso*Butylbenzyl alcohol (100 g.) and 33% sulphuric acid (w/w) (250 ml.) were refluxed with vigorous stirring for 3 hr. The product was taken up in ether, and the ethereal solution was washed with water until neutral, dried ($Na_2SO_4$), and distilled from 2 : 5-di-*tert.*-butylquinol (2 g.), finally under reduced pressure, giving 3-methyl-1-phenylbutene (64 g., 72%), b. p. 100—102°/24 mm., $n_D^{25}$ 1·5270 (Klages [5] gives b. p. 102—103°/26 mm., $n_D^{20}$ 1·5248). The olefin, in absolute ethanol (80 ml.), was hydrogenated at 60°/50 atm. in presence

[1] Lauer and Lockwood, *J. Amer. Chem. Soc.*, 1954, **76**, 3974.
[2] Ipatieff and Schmerling, *ibid.*, 1938, **60**, 1476.
[3] Hass and Bender, *ibid.*, 1949, **71**, 3482.
[4] Storrie, *J.*, 1937, 1746.
[5] Klages, *Ber.*, 1904, **37**, 2301.

of Raney nickel (10 g.), giving *iso*pentylbenzene (51 g., 80%), b. p. 86—88°/16 mm., $n_D^{25}$ 1·4850. Hass and Bender [3] give b. p. 83—84°/16 mm., $n_D^{20}$ 1·4862.

o- *and* p-*Nitroisopentylbenzenes*. An ice-cold mixture of concentrated nitric acid (135 g., 1·5 mol.) and concentrated sulphuric acid (250 g., 2·5 mol.) was added dropwise with stirring and cooling to *iso*pentylbenzene (150 g.), at such a rate that the temperature did not exceed 10°. Stirring was continued for a further 1 hr., during which the mixture was allowed to reach room temperature. The product, isolated with ether, yielded on fractionation o-*nitroisopentylbenzene* (81 g., 41%), b. p. 94—96°/0·5 mm., $n_D^{25}$ 1·5158 (Found: C, 68·6; H, 7·5; N, 6·95. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8; N, 7·25%), and p-*nitroisopentylbenzene* (90 g., 45%), b. p. 110°/0·5 mm., $n_D^{25}$ 1·5222 (Found: C, 68·6; H, 7·5; N, 7·3%). Oxidation of the two nitro-compounds with 25% nitric acid overnight at 175—180° gave *o*- and *p*-nitrobenzoic acids respectively.

o-iso*Pentylaniline*. Concentrated hydrochloric acid (3 ml.) was added at intervals of 2 hr. to a boiling, vigorously stirred mixture of iron powder (65 g.) and *o*-nitro*iso*pentylbenzene (75 g.) in ethanol (500 ml.). After 12 hr. the mixture was basified and steam-distilled, and the product was isolated with ether, giving the amine (56 g., 90%), b. p. 90°/1 mm., $n_D^{25}$ 1·5257 (Found: C, 80·9; H, 10·0; N, 8·2. Calc. for $C_{11}H_{17}N$: C, 80·9; H, 10·5; N, 8·6%). Lauer and Lockwood [1] give b. p. 128—131°/15 mm., $n_D^{25}$ 1·5310. The *acetyl derivative* formed needles (from aqueous ethanol), m. p. 93—94° (Found: C, 76·0; H, 9·4; N, 7·0. $C_{13}H_{19}ON$ requires C, 76·05; H, 9·3; N, 6·8%). The benzoyl derivative formed needles (from ethanol), m. p. 151—152° (Found: C, 81·3; H, 7·8; N, 5·3. Calc. for $C_{18}H_{21}ON$: C, 80·9; H, 7·9; N, 5·2%) Lauer and Lockwood [1] give m. p. 154—154·5°.

p-iso*Pentylaniline*. The amine, prepared in 93% yield analogously to the *ortho*-isomer, had b. p. 96°/1 mm., $n_D^{25}$ 1·5251. The acetyl derivative formed plates (from alcohol), m. p. 115—116° (Found: C, 75·9; H, 9·5; N, 7·1%), and the benzoyl derivative formed plates (from alcohol), m. p. 150—151° (Found: C, 80·6; H, 7·8; N, 5·4%). Hickinbottom [6] records m. p. 115—115·5° and m. p. 151—153° respectively for these derivatives. The m. p. of the benzoyl derivative was depressed on admixture with *o*-benzamido*iso*pentylbenzene.

4-*Acetamido*-3-*bromoisopentylbenzene*. Bromine (10·3 g.) in acetic acid (10 ml.) was added dropwise to a solution of *p*-acetamido*iso*pentylbenzene (11 g.) in acetic acid (20 ml.) at 40°. The temperature rose and was kept at 50—55° for 1 hr. Isolation in the usual way gave the 3-*bromo-compound* (13·4 g., 88%) as colourless plates (from aqueous ethanol), m. p. 83·5—84° (Found: C, 55·0; H, 6·1; N, 4·8. $C_{13}H_{18}ONBr$ requires C, 54·9; H, 6·4; N, 4·9%).

2-*Bromo*-4-iso*pentylaniline*. The above acetamido-derivative (13 g.) was refluxed with ethanol (20 ml.) and concentrated hydrochloric acid (20 ml.) for 2 hr. The resulting *bromo-amine* (9·75 g., 88%), $n_D^{25}$ 1·5504, was distilled in high vacuum in a short-path still at 100° (bath temp.) (Found: N, 5·6. $C_{11}H_{16}NBr$ requires N, 5·8%).

5-*Nitro*-2-iso*pentylaniline*. An ice-cold mixture of concentrated nitric acid (6·35 g., 1 mol.) and concentrated sulphuric acid (30 g.) was added dropwise with stirring to a solution of *o-iso*-pentylaniline (11·5 g.) in concentrated sulphuric acid (170 g.) at 0°. The mixture was stirred for 3 hr., then poured on powdered ice (300 g.). Treatment with alkali gave the *nitro-amine* (7·8 g., 50%) which crystallised from aqueous methanol as orange-yellow prisms, m. p. 70—71° (Found: C, 63·3; H, 7·6; N, 13·4. $C_{11}H_{16}O_2N_2$ requires C, 63·4; H, 7·7; N, 13·45%).

Reduction with tin and hydrochloric acid in ethanol, followed by acetylation as usual, gave 2 : 4-diacetamido*iso*pentylbenzene,[2,3] m. p. and mixed m. p. 219—219·5°.

p-iso*Pentylbenzoic acid*. Sodium nitrite (7·6 g.) in water (15 ml.) was added dropwise to a cooled suspension of *p-iso*pentylaniline (16·3 g.) in 46% hydrobromic acid (70 g.) and water (10 ml.), the flask being stoppered and well shaken after each addition of the nitrite solution. Copper bronze (2 g.) was added and the mixture was warmed gently until a vigorous reaction set in. When this subsided the mixture was heated at 100° for 1 hr. and then steam-distilled. The resulting bromo-compound (11·6 g., 51%), b. p. 96—98°/0·7 mm., $n_D^{25}$ 1·5210, was converted into the Grignard reagent in the usual manner and poured on an excess of powdered solid carbon dioxide. The syrupy product was treated with hydrochloric acid, and the ethereal layer was separated and extracted with sodium carbonate solution. Acidification of the extract gave p-iso*pentylbenzoic acid* (5 g.) which crystallised from hexane as needles, m. p. 128·5—129° (Found: C, 75·4; H, 8·15. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). The p-*bromophenacyl ester* formed plates, m. p. 124—124·5° (Found: C, 62·0; H, 5·7. $C_{20}H_{21}O_3Br$ requires C, 61·7; H, 5·4%); the *amide*, plates, m. p. 136—137° (Found: C, 75·2; H, 8·5; N, 7·0. $C_{12}H_{17}ON$

[6] Hickinbottom, *J.*, 1932, 2396.

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requires C, 75·35; H, 9·0; N, 7·3%); and the *anilide*, plates, m. p. 137·5—138° (Found: C, 81·1; H, 7·5; N, 5·2. $C_{18}H_{21}ON$ requires C, 80·9; H, 7·9; N, 5·2%).

o-iso*Pentylbenzoic acid*. This *acid*, prepared from *o-iso*pentylaniline analogously to the *para*-isomer, was distilled *in vacuo* forming a wax-like solid, m. p. 45·5—46° (Found: C, 75·1; H, 8·3%). The p-*bromophenacyl ester* formed needles, m. p. 59·5—60° (Found: C, 61·7; H, 5·5%), and the *anilide* formed plates, m. p. 102—103° (Found: C, 81·5; H, 7·6; N, 5·2%).

m-iso*Pentylbenzoic acid*. 2-Bromo-4-*iso*pentylaniline (9·7 g.) in concentrated hydrochloric acid (12·5 ml.) and water (25 ml.) was diazotised, at 5°, by the slow addition of sodium nitrite (3 g.) in water (15 ml.). Hypophosphorous acid (50%, 100 ml.) was added, and the mixture was set aside overnight at 0°. The oil which separated was isolated with ether, distilled *in vacuo* in a short-path still and converted into the Grignard reagent. Carbonation, as before, yielded m-iso*pentylbenzoic acid* (3 g.) which crystallised from hexane as prisms, m. p. 59—60° (Found: C, 75·0; H, 8·2%). The p-*bromophenacyl ester* formed woolly needles, m. p. 64—64·5° (Found: C, 62·1; H, 5·5%); the *amide*, needles, m. p. 105—106° (Found: C, 76·0; H, 8·7; N, 7·2%); and the *anilide*, needles, m. p. 78—78·5° (Found: C, 81·4; H, 7·7%).

The author thanks Dr. A. D. Campbell, University of Otago, for the microanalyses.

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## 421. *Some Reactions of* 1 : 2-*Epithio-octane.*

By C. G. MOORE and M. PORTER.

RECENT examination [1] of the polysulphide obtained from sulphur and oct-1-ene at 140° necessitated a study of the reactivity of the epithio-group in 1 : 2-epithio-octane (I) towards heat and the nucleophilic reagents $AlH_4^-$ and $HS^-$. The episulphide (I) was prepared by reaction of 1 : 2-epoxyoctane [2] with thiourea, the procedure used [3] being designed to minimise alkali-catalysed polymerization of the product.

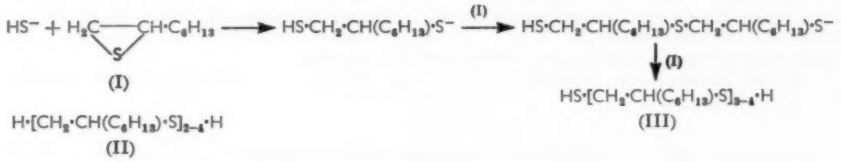
The susceptibility of episulphides to polymerization becomes less marked in the higher members of the series; [4] thus the epithio-octane (I) is stable at room temperature in the absence of acids or alkalis and is little changed after 1 hr. *in vacuo* at 140°. Heating for 5 hr. at 140° causes appreciable increase in molecular weight, but spectral evidence suggests that this is due to decomposition into oct-1-ene and sulphur followed by reaction of these to form a polysulphide. Thermal decomposition into olefin and sulphur has been observed similarly with 1 : 2-epithio-1-phenylethane [5] and with 1 : 2-epithio*cyclo*hexane.[6]

Reduction of episulphides with lithium aluminium hydride gives [7] thiols in about 75% yield, the sulphur atom remaining bound to the more substituted carbon atom. Contrary to this finding, reduction of the epithio-octane (I) gave only a small amount of the expected octane-2-thiol, the major product being a polymer (II), probably formed by anionic polymerization initiated by attack of the $AlH_4^-$ ion on the episulphide. This polymer was similar in structure to that formed by action of alkali; the latter polymer is only slightly attacked by lithium aluminium hydride. There was no evidence for any anomalous hydrogenolysis involving removal of sulphur and formation of oct-1-ene in the manner in which butyl- or phenyl-lithium removes the sulphur atom from episulphides [7] or lithium aluminium hydride removes the oxygen atom from oxazirans.[8]

Culvenor, Davies, and Heath [4] found that attack of $HS^-$ and $RS^-$ ions on episulphides

[1] Bateman, Glazebrook, Moore, Porter, Ross, and Saville, *J.*, in the press.
[2] Swern, Billen, and Scanlan, *J. Amer. Chem. Soc.*, 1946, **68**, 1504.
[3] Bordwell and Andersen, *ibid.*, 1953, **75**, 4959.
[4] Culvenor, Davies, and Heath, *J.*, 1949, 282.
[5] Guss and Chamberlain, *J. Amer. Chem. Soc.*, 1952, **74**, 1342.
[6] Mousseron *et al.*, *Bull. Soc. chim. France*, 1948, 84.
[7] Bordwell, Andersen, and Pitt, *J. Amer. Chem. Soc.*, 1954, **76**, 1082.
[8] Emmons, *ibid.*, 1957, **79**, 5739.

produces vicinal dithiols and mercapto-sulphides, respectively, together with polymeric material. In corroboration of this, reaction of potassium hydrogen sulphide with the episulphide (I) gave a small yield of octane-1 : 2-dithiol and considerable polymer (III) formed by the process: [9]




*Experimental.*—**1 : 2-*Epithio-octane*** (I). The episulphide was prepared by reaction of 1 : 2-epoxyoctane (from oct-1-ene by perbenzoic acid oxidation [10]) with thiourea as described by Bordwell and Andersen.[3] Fractionation of the product gave unchanged epoxide (7%), episulphide (I) contaminated with some epoxide (78%) (Found: C, 68·5; H, 11·3; S, 18·1%), and residual pale yellow polymer (15%) (Found: C, 67·35; H, 11·35; S, 20·5%; *M*,* 2000—3000). Refractionation afforded pure **1 : 2-*epithio-octane***, b. p. 83°/5 mm., $n_D^{20}$ 1·4702 (Found: C, 66·95; H, 10·9; S, 22·2%; *M*,* 142. $C_8H_{16}S$ requires C, 66·6; H, 11·2; S, 22·2%; *M*, 144), showing principal infrared bands (measured on the Hilger H. 800 double-beam instrument as a 100μ-thick film) at ~1445, 1371, 1296, 1263, 1107, 1030, 905, 716 cm.$^{-1}$.

*Thermal stability of episulphide* (I). The episulphide (I) was indefinitely stable at room temperature but after 1 hr. *in vacuo* at 140° it had become yellow (Found: S, 21·9%; *M*,* 148, 151). Similar treatment for 5 hr. gave a red-brown product (Found: S, 21·7%; *M*,* 218, 214) which did not react with lead acetate. The infrared spectra of both products were similar to that of pure episulphide (I) but additional bands due to vinylic unsaturation were present. Estimates, as oct-1-ene, gave results of 1% and 8%, respectively. Another band at 970 cm.$^{-1}$ was ascribed to a skeletal vibration of a sulphurated octane grouping, since octane-1- and -2-thiol and octane-1 : 2-dithiol all show this absorption.[1] The ultraviolet absorption spectra indicated the presence of elemental sulphur or polysulphide groups.

*Reduction of episulphide* (I). The compound (1·425 g.) was reduced with lithium aluminium hydride (0·9 g.) as described by Bateman *et al.*[1] No hydrogen sulphide was evolved and fractionation of the product gave: (i) mainly octane-2-thiol (0·28 g.), b. p. 66—69°/23 mm. (Found: C, 67·3; H, 12·35; S, 20·15. Calc. for $C_8H_{18}S$: C, 65·7; H, 12·4; S, 21·9%), identified as **2 : 4-dinitrophenyl 1-methylheptyl sulphide**, m. p. and mixed m. p. 49—49·5° (after 3 recrystallisations from ethanol) (Found: C, 53·9; H, 6·5; N, 8·9. Calc. for $C_{14}H_{20}O_4N_2S$: C, 53·8; H, 6·45; N, 9·0%); (ii) a liquid (0·33 g.), b. p. 105—108°/0·05 mm. (Found: C, 66·2; H, 11·7; S, 21·8%; *M*,* 307, 286. Calc. for $C_{16}H_{34}S_2$: C, 66·1; H, 11·8; S, 22·1%; *M*, 289), containing thiol groups (infrared spectrum); (iii) a yellow residue (0·44 g.) [Found: C, 66·9; H, 11·6; S, 21·5%; *M*,* 466, 448. This corresponds to $(C_8H_{16\cdot5}S_{1\cdot0})_{3\cdot2}$], whose infrared spectrum was similar to that of the episulphide polymer isolated during the preparation of the monomer (I); thiol groups were also present.

*Action of potassium hydrogen sulphide on episulphide* (I). The episulphide (1·367 g.) was shaken for 3 days with a solution of potassium hydrogen sulphide in ethanol [prepared by saturating a solution of potassium hydroxide (0·94 g.) in ethanol (10 ml.) at 0° with hydrogen sulphide]. The bulk of the ethanol was removed at low pressure and excess of aqueous sodium hydroxide was added to the residue, which was then extracted with light petroleum (b. p. <40°; 3 × 30 ml.), washed with water, and dried ($Na_2SO_4$). Removal of the solvent gave an oil (1·20 g.) [Found: C, 63·8; H, 11·0; S, 25·1%; *M*,* 559, 560. This corresponds to $(C_8H_{16\cdot4}S_{1\cdot2})_{3\cdot7}$]. The infrared spectrum showed the presence of ~1—2 thiol groups per molecule. The alkaline solution was worked up in the same way to give impure octane-1 : 2-dithiol (0·05 g.) (Found: C, 56·0, 56·2; H, 9·7, 9·6; S, 33·0. Calc. for $C_8H_{18}S_2$: C, 53·9; H, 10·2; S, 36·0%), identified by its infrared spectrum.

*Stability of the polymer towards lithium aluminium hydride.* The polymer (0·885 g.) obtained

* All molecular weights thus recorded were obtained ebullioscopically in benzene.

[9] Cf. Meade and Woodward, *J.*, 1948, 1894.
[10] Swern, in " Organic Reactions," Vol. VII, John Wiley, London, 1953, p. 396.

XUM

as by-product in the preparation of episulphide (I) was treated with lithium aluminium hydride (1·73 g.) in tetrahydrofuran (20 ml.) for 5 hr. in the usual way. The product (0·744 g.) was a viscous liquid, not distillable below 120°/17 mm. (Found: C, 67·45; H, 11·3; S, 19·3%; *M*,* 1220, 1540).

We thank Mr. G. M. C. Higgins and Mr. M. B. Evans for the spectroscopic data.

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48—56, TEWIN ROAD, WELWYN GARDEN CITY, HERTS. [*Received, January 1st*, 1958.]

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## 422. *The Solubility of Arsenious Oxide in Aqueous Hydrochloric Acid at 25°.*

By I. A. MENZIES and L. W. OWEN.

THE solubility of arsenious oxide in hydrochloric acid solutions at 15° was determined by Wood [1] and at 25° by Ghiron and Mangili.[2] More extensive studies were made of this system (0—8m-hydrochloric acid) and of the system arsenious oxide–sodium hydroxide–water by Garrett, Holmes, and Laube,[3] whose data have now been extended to 15m-hydrochloric acid.

The results (expressed in moles per kg. of water; see Table) are in good agreement with those of Garrett, Holmes, and Laube. Comparison of the present values with those of Wood indicate the lower solubility at 15°.

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| HCl ... | $0.286_1$ | $1.25_4$ | $2.50_4$ | $3.45_2$ | $5.27_4$ | $6.70_4$ | $7.17_1$ | $9.14_7$ | $10.4_9$ | $12.6_7$ | $14.7_2$ |
| $As_2O_3$ | $0.083_4$ | $0.081_5$ | $0.075_5$ | $0.076_9$ | $0.120_2$ | $0.254_9$ | $0.317_4$ | $0.734_3$ | $1.03_5$ | $1.58_4$ | $2.04_1$ |

The minimum in the solubility curve occurs at a hydrochloric acid molality of 2·5—3·5 and is understandable on the basis of interaction between (*a*) chemical and physical salting-out and (*b*) formation of arsenious oxide–hydrochloric acid compounds. Chemical salting-out is the result of repression of dissociations of the type $As_2O_3,xH_2O \rightleftharpoons [AsO_3^{3-}][3H^+] + As_2O_3,yH_2O$ by hydrochloric acid: physical salting-out results from the lowering of the activity of the water by hydrochloric acid.

The rapid increase in solubility at higher hydrochloric acid concentrations is undoubtedy caused by compound formation between arsenious oxide and hydrochloric acid. The formation of arsenious chlorides and oxychlorides is most probable and arsenic trichloride has been isolated from such solutions by distillation.[4]

*Experimental.*—" AnalaR " chemicals were used, arsenious oxide being recrystallised from hydrochloric acid as described by previous authors.[1,5] Redistilled water was used.

The concentration of each hydrochloric acid solution was determined by titration against a solution of sodium hydroxide previously standardised by titration with a solution of hydrochloric acid prepared from constant-boiling hydrochloric acid. Excess of arsenious oxide was added to each acid solution in a conical borosilicate glass flask at 25° ± 0·01°. The suspension was stirred until no further increase in arsenic concentration of the solution was detectable over two periods of 6 hr. each. Then the excess of arsenious oxide was filtered off and the solution neutralised with sodium carbonate. The solution was then made slightly acid. 2·5 g. of sodium

[1] Wood, *J.*, 1908, 411.
[2] Ghiron and Mangili, *Gazzetta*, 1935, **65**, 1244.
[3] Garrett, Holmes, and Laube, *J. Amer. Chem. Soc.*, 1940, **62**, 2024.
[4] Partington, " General and Inorganic Chemistry," MacMillan & Co., London, 1951.
[5] Garrett and Howell, *J. Amer. Chem. Soc.*, 1939, **61**, 1730.

hydrogen carbonate were added and the solution was titrated with 0·1N-iodine with starch as indicator.

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UNITED KINGDOM ATOMIC ENERGY AUTHORITY, MATERIALS RESEARCH DIVISION,
A.W.R.E., ALDERMASTON, BERKS. [*Received, January 6th*, 1958.]

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## 423. *Non-ionic Surface-active Agents. Part II.* The Synthesis of Some Polyoxyethylene Glycol Monohexyl Ethers.*

By B. A. MULLEY.

FOR a study of non-ionic surface-active agents a range of pure compounds was required with lipophilic and hydrophilic properties. This Note describes the preparation of polyoxyethylene glycol monohexyl ethers with two to six ethylene oxide units per molecule. The compounds with two and three ethylene oxide units severally are almost insoluble in water at 20°. Higher members are soluble in water at this temperature and have a hydrophilic nature which increases with the number of oxide units per molecule.

A few reports [1] have previously appeared describing homogeneous compounds of this type although in the first two cases no experimental details were given. The Williamson ether synthesis was chosen as a synthetic route in the present work: $C_6H_{13}Br + NaO\cdot[CH_2\cdot CH_2O]_n\cdot H \longrightarrow C_6H_{13}\cdot O\cdot[CH_2\cdot CH_2\cdot O]_n\cdot H \rightleftharpoons C_6H_{13}\cdot O\cdot[CH_2\cdot CH_2\cdot O]_{n-1}\cdot CH_2\cdot CH_2Cl$. To minimise the formation of dialkyl ethers approximately eight equivalents of the glycol were used to one of sodium, so that mainly monosodium derivatives were obtained. Small amounts of the diethers were probably still produced but these were not isolated. The monoethers with $n = 2$ and 3 were prepared in this way from di- and tri-ethylene glycol and with thionyl chloride in the presence of pyridine gave the derived chloro-compounds. These condensed readily with the appropriate monosodium derivative of diethylene or triethylene glycol to give the monoethers with $n = 4$, 5, and 6.

The cooling curves of the compounds showed a constant temperature at the f. p. and the sudden drop as the solids started to cool, which is characteristic of pure substances.

*Experimental.*—Microanalyses were by Mr. G. S. Crouch, School of Pharmacy, University of London. Hydroxyl groups were determined by the method given by Curme and Johnston.[2] *n*-Hexyl bromide was obtained from Eastman Kodak Co.

**3 : 6-*Dioxadodecan*-1-*ol*** ($n = 2$). Sodium (20·9 g.) was dissolved in diethylene glycol (385·6 g.), and the solution heated with *n*-hexyl bromide (150 g.) at ~200° for several hours. Benzene (750 ml.) was added and the mixture extracted with water (3 × 100 ml.). The theoretical quantity of sodium bromide was found in the water fractions. Evaporation of the benzene from the organic layer and fractional distillation of the residue gave 3 : 6-dioxadodecan-1-ol (93 g.), b. p. 140—141°/16 mm., f. p. −33·6° (Found: C, 62·2; H, 11·9; OH, 9·25. Calc. for $C_{10}H_{22}O_3$: C, 63·1; H, 11·6; OH, 8·9%). Chakhovskoy, Martin, and Van Nechel [1] give b. p. 115—115·6°/2 mm., f. p. −40·2°.

**1-*Chloro*-3 : 6-*dioxadodecane*** ($n = 2$). To the above alcohol (60 g.) and pyridine (20·5 g.), thionyl chloride (75 g.) was added in portions and the whole refluxed for 1½ hr. Excess of

* Part I, *J. Pharm. Pharmacol.*, 1956, **8**, 774.

[1] Brandner, Lockwood, Nagel, and Russell, F.I.A.T. Final Report, No. 1141, p. 11; Goto, Sugano, and Koizumi, *Bull. Inst. Chem. Res., Kyoto Univ.*, 1953, **31**, 305; Chakhovskoy, Martin, and Van Nechel, *Bull. Soc. chim. belges*, 1956, **65**, 453, and references there cited; Gingras and Bayley, *Canad. J. Chem.*, 1957, **35**, 599.

[2] Curme and Johnston, "Glycols," Reinhold Pub. Corp., New York, 1952, p. 333.

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thionyl chloride was destroyed with water (40 ml.), and benzene (100 ml.) was added. The organic layer was washed with sodium hydrogen carbonate solution and with water, dried ($MgSO_4$), and evaporated. Distillation then gave 1-*chloro*-3 : 6-*dioxadodecane* (49 g.), b. p. 126°/14 mm. (Found: C, 57·1; H, 10·0; Cl, 17·5. $C_{10}H_{21}O_2Cl$ requires C, 57·5; H, 10·1; Cl, 17·0%).

3 : 6 : 9-*Trioxapentadecan*-1-*ol* ($n = 3$).—A solution from sodium (7 g.) and triethylene glycol (182 g.) was treated with *n*-hexyl bromide (50 g.) as described above. Water (250 ml.) and light petroleum (b. p. 100—120°; 200 ml.) were added, and the two-phase mixture heated to 70°. The organic layer was then washed with water (50 ml.) at 70°. Distillation, after removal of the solvent, gave 3 : 6 : 9-trioxapentadecan-1-ol (34 g.), b. p. 152—153°/5 mm., f. p. −26·1° (Found: C, 62·2; H, 11·5; OH, 7·1. Calc. for $C_{12}H_{26}O_4$: C, 61·5; H, 11·2; OH, 7·3%). Chakhovskoy and his co-workers [1] gave b. p. 150—150·4°/2 mm., f. p. −34·5°. Sodium bromide (25·2 g.) was found in the water-fractions obtained from the extraction procedure.

1-*Chloro*-3 : 6 : 9-*trioxapentadecane* ($n = 3$). The alcohol ($n = 3$) (20 g.) with thionyl chloride (15·3 g.) in the presence of pyridine (6·75 g.) gave the *chloride* (16·2 g.), b. p. 137—141°/3·5 mm. (Found: C, 56·6; H, 10·1; Cl, 14·0. $C_{12}H_{25}O_3Cl$ requires C, 57·0; H, 10·0; Cl, 14·0%).

3 : 6 : 9 : 12-*Tetraoxaoctadecan*-1-*ol* ($n = 4$). 1-Chloro-3 : 6-dioxadodecane ($n = 2$) (50 g.) was heated with the derivative made by dissolving sodium (5·5 g.) in diethylene glycol (101·5 g.), and the precipitated sodium chloride was removed. Distillation of the filtrate gave 3 : 6 : 9 : 12-tetraoxaoctadecan-1-ol (36·6 g.), b. p. 158—159°/1·5 mm., f. p. −11·9° (Found: C, 60·1; H, 11·1; OH, 6·2. Calc. for $C_{14}H_{30}O_5$: C, 60·4; H, 10·8; OH, 6·1%). Chakhovskoy *et al.*[1] gave b. p. 134—134·2°/0·005 mm., f. p. −18·1°. The sodium chloride filtered from the reaction mixture, together with that found in the residue after distillation, was in theoretical yield.

3 : 6 : 9 : 12 : 15-*Pentaoxaheneicosan*-1-*ol* ($n = 5$) (30·5 g.) was obtained from 1-chloro-3 : 6-dioxadodecane ($n = 2$) (40 g.), triethylene glycol (114·8 g.), and sodium (4·4 g.) and had b. p. 163—165°/0·15 mm., f. p. −3·3° (Found: C, 59·7; H, 10·5; OH, 5·35. $C_{16}H_{34}O_6$ requires C, 59·6; H, 10·6; OH, 5·3%) [with sodium chloride (11·06 g.)].

3 : 6 : 9 : 12 : 15 : 18-*Hexaoxatetracosan*-1-ol ($n = 6$) prepared (12 g.) as in the last two cases, from the chloride ($n = 3$) (15·2 g.), triethylene glycol (36 g.), and sodium (1·8 g.), had b. p. 192—194°/0·15 mm., f. p. 1·2° (Found: C, 58·9; H, 10·7; OH, 4·9. $C_{18}H_{38}O_7$ requires C, 59·0; H, 10·4; OH, 4·6%); the sodium chloride amounted to 3·33 g.

*Cooling curves.* About 5 g. of the compounds were used in a lagged tube immersed in a bath maintained about 10° below the f. p.

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## 424. *Acidity-dependence of Decomposition of Cumene Hydroperoxide.*

By A. W. DE RUYTER VAN STEVENINCK.

THE acid-catalyzed decomposition of cumene hydroperoxide has been reported to be of first-order with respect to the concentration of both hydroperoxide and acid when the reaction is carried out in 50% (w/w) acetic acid with toluene-*p*-sulphonic acid as the catalyst and the ionic strength is maintained constant by the addition of lithium chloride.[1] Using the same solvent and sulphuric acid as the catalyst, Wichterle and Cefelin [2] established the same relation for the reaction in absence of neutral salts.

When carrying out the reaction in 50% (w/w) ethanol, the catalyst being perchloric acid of various concentrations, the author found that the second-order rate constant

[1] Seubold and Vaughan, *J. Amer. Chem. Soc.*, 1953, **75**, 3790.
[2] Wichterle and Cefelin, *Chem. Listy*, 1957, **51**, 747.

$k_{II}$, defined by $-d[R\cdot O\cdot OH]/dt = k_{II}[R\cdot O\cdot OH][HClO_4]$, increases with increasing acid concentration, as shown by the data in Table 1.

TABLE 1. *Influence of acid concentration on the second-order rate constant of cumene hydroperoxide decomposition, in* 50% (*w*/*w*) *ethanol, at* 50°. $[R\cdot O\cdot OH] = 0{\cdot}20$M.

| $HClO_4$ (moles/l.) | 0·048 | 0·098 | 0·196 | 0·283 | 0·382 |
|---|---|---|---|---|---|
| $k_{II} \times 10^5$ (l. mole$^{-1}$ sec.$^{-1}$) | 4·9 | 5·5 | 6·9 | 7·7 | 9·4 |

In order to obtain more information on this effect, a series of rate measurements was carried out in which the concentration of perchloric acid was kept constant, whilst increasing quantities of lithium perchlorate were added. Determination of the acetone and phenol produced showed that the addition of this salt has no influence on the composition of the product and only enhances the reaction velocity (Table 2).

TABLE 2. *Influence of addition of salt on the second-order rate constant of cumene hydroperoxide decomposition, in* 50% (*w*/*w*) *ethanol, at* 50°. $[R\cdot O\cdot OH] = 0{\cdot}12$M, $[HClO_4] = 0{\cdot}19$N.

| $[ClO_4^-]$ (g.-ions/l.) | 0·19 | 0·30 | 0·50 | 0·70 | 0·90 | 1·10 | 1·30 | 1·54 | 1·75 | 2·00 |
|---|---|---|---|---|---|---|---|---|---|---|
| $k_{II} \times 10^5$ (l. mole$^{-1}$ sec.$^{-1}$) | 6·9 | 8·2 | 11·4 | 14·3 | 19·0 | 25·1 | 33·7 | 47·5 | 63·5 | 88·0 |

Examination of the results given in Table 2 shows a linear dependence of log $k_{II}$ on the total electrolyte concentration. Similarly, a determination of the values of Hammett's acidity function [3] $H_0$ under the conditions of the kinetic experiments, *p*-nitroaniline being used as the indicator base, demonstrated that $H_0$ depends linearly on the total electrolyte

TABLE 3. *Influence of the electrolyte concentration on acidity function* $H_0$.

| $[ClO_4^-]$ (g.-ions/l.) | 0·190 | 0·689 | 1·186 | 1·686 | 2·184 |
|---|---|---|---|---|---|
| $H_0$ | 1·72 | 1·53 | 1·31 | 1·10 | 0·89 |

concentration (Table 3). From this result, in combination with the above-mentioned linear dependence of log $k_{II}$ on the total electrolyte concentration, it follows that log $k_{II}$ depends linearly on $H_0$, a plot showing a straight line with slope −1·45. According to Zucker and Hammett [4] such a linear dependency on $H_0$ rather than on $-\log [H_3O^+]$ suggests that the formation of the transition state is a unimolecular rather than a bimolecular process involving a solvent (water) molecule.

In order to investigate whether this relationship is specific for the $HClO_4$–$LiClO_4$ system, the same experiments were carried out with two other acid–salt pairs, *viz.*, HCl–LiCl and *p*-$CH_3\cdot C_6H_4\cdot SO_3H$–*p*-$CH_3\cdot C_6H_4\cdot SO_3Li$. Here, too, straight lines were obtained on plotting log $k_{II}$ against $H_0$, the slopes being −1·01 and −0·76, respectively. Deviations from a slope of unity—predicted by Zucker and Hammett—are probably caused by the use of an only partially aqueous solvent.

The apparent difference in behaviour between the acid-catalyzed cumene hydroperoxide decomposition in aqueous acetic acid and that in aqueous ethanol—the former showing correlation with acid concentration and the latter with acidity function—does not imply a difference in reaction mechanism. Wichterle and Cefelin [2] have established a proportionality between $H_0$ and $-\log [H_3O^+]$ on determining $H_0$ in solutions of sulphuric acid in 50% (w/w) acetic acid. Very probably the greater proton affinity of ethanol than of acetic acid causes deviations to occur between $H_0$ and $-\log [H_3O^+]$ at much lower acid concentrations.

KONINKLIJKE/SHELL-LABORATORIUM, AMSTERDAM
(N.V. DE BATAAFSCHE PETROLEUM MAATSCHAPPIJ). [*Received, November 29th,* 1957.]

[3] Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 267.
[4] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791.

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## 425. *Decamethylene Dibromide.*

By E. P. Taylor.

Kaluszyner [1] has described an easy and inexpensive preparation of tetramethylene dibromide by reaction of sodium bromide and concentrated sulphuric acid with tetrahydrofuran. Published preparations of decamethylene dibromide include reaction of decamethylene glycol with fuming hydrobromic acid in a sealed tube [2] (yield 98%), with dry hydrogen bromide [3, 4] (yield 85—90%), or with hydrobromic–sulphuric acid [5] (yield 67%). We have found the simplest preparation to be reaction of the glycol with sodium bromide and concentrated sulphuric acid, giving yields of the order of 80%.

*Experimental.*—Concentrated sulphuric acid (194 g.) was added dropwise to a well-stirred mixture of sodium bromide (150 g., 1·45 moles), water (130 ml.), and decamethylene glycol (63 g., 0·36 mole). The stirred mixture was then gently refluxed for 6 hr. and then allowed to cool, an equal volume of water added, and the solution extracted with ether. The extract was washed with water, sodium hydrogen carbonate solution, sodium thiosulphate solution, and water, and dried ($Na_2SO_4$), the solvent removed, and the residue distilled *in vacuo*, giving decamethylene dibromide (88 g., 81%), b. p. 166—168°/12 mm., plates, m. p. 28°.

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Ware, Herts.

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[1] Kaluszyner, *J. Org. Chem.*, 1957, **22**, 834.
[2] Franke and Hankam, *Monatsh.*, 1910, **31**, 177.
[3] Chuit, *Helv. Chim. Acta*, 1926, **9**, 264.
[4] Carothers, Hill, Kirby, and Jacobson, *J. Amer. Chem. Soc.*, 1930, **52**, 5279.
[5] Price, Guthrie, Herbrandson, and Peel, *J. Org. Chem.*, 1946, **11**, 281.

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## Reactions of Free Radicals in the Gas Phase

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